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United Services Section

President—Sir LIONEL WHITBY, C.V.O., M.C., M.D., F.R.C.P.

[October 7, 1954]

Some Aspects of Aviation Medicine in Regard to Radiological Hazards

By Group Captain DENIS WILSON, A.F.C., M.R.C.S., F.F.R., and
Wing Commander G. H. DHENIN, A.F.C., G.M., M.B., Ch.B.

Group Captain Denis Wilson:

In dealing with this question I shall confine my remarks to those radiation hazards that may be encountered during peace. It will be realized, of course, that some of the points which may appear to be omitted or passed over are treated in this way for security reasons.

When I first started to be involved in this type of work five years ago the subject was almost a closed book on this side of the Atlantic and it seemed possible that radiation hazards to aircraft crews might be a real danger in the future even in peacetime. It was thought that these hazards might come from

- (a) The ionization effect of cosmic radiation on high-flying aircraft.
- (b) Inhalation and ingestion hazard on high-flying passenger aircraft following a series of atomic bomb tests a long way away.
- (c) Hazards both of primary radiation and inhalation and ingestion for military aircraft sampling during these tests.

(a) The hazard due to cosmic radiation has been the subject of much research and if many of the major problems of the origin of the cosmic rays and their actual components are still unsolved those of the radiation hazards are less uncertain.

Cosmic radiation can be recognized at earth level and even considerably below the earth's surface. It is increased in intensity by a factor of about 15 at 75,000 feet in northern latitudes and more in the polar areas and then, probably as a result of a combination of the geomagnetic field and the earth's shadow, decreases to about 150,000 feet when it is again increased until at 8,000 miles it is presumed to reach its maximum. At this maximum, ionization dosage will be substantially greater in the denser materials such as aircraft or rocket ships and that includes the occupants inside. This is due to the transition effect.

So that we now know that unless an aircraft is going to spend many days at over 75,000 feet and beyond there is no perceptible radiation hazard to the crew. As this, at present, is confined to legendary characters like Jet Morgan of B.B.C. fame and his colleagues in papers like the *Eagle* we can dismiss it as a present danger.

- (b) In the second case it was felt that high-flying transatlantic aircraft might by a combination

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of circumstances fly for many hours in a layer containing comparatively fresh fission products from a series of bomb tests. It is known that bombs of the same approximate energy let off in the same area and under similar meteorological conditions will send their clouds to approximately the same height and whilst a proportion of these clouds fall out, the particle sizes are often so small that they remain in the sky for many days. It is theoretically possible that an aircraft flying on a standard course at an altitude around 45,000 feet for some hours might pick up and push into its pressurized cabin (and its passengers) measurable amounts of fission products. The medico-legal implications of a jet airliner full of rich and influential business men getting in such a position are full of intriguing possibilities! To date, however, we have not had any transatlantic passenger aircraft capable of flying at these altitudes and the problem has not arisen, but with the advent of the Comet III and the arrival of new nuclear weapons of fantastic power on the testing grounds the problem is not so very academic. The answer, of course, is simple, since cabin air can be filtered easily and effectively with little penalty in either weight or bulk. To date, however, no passenger aircraft carries these filters.

(c) Thirdly, it was felt that aircraft closely concerned with tests for scientific or military reasons were bound to get a fairly high degree of irradiation. The only information we could find was some calculations that were a little alarming to say the least, but since the scientist who produced these was "out of reach" we could not discuss them further with him, but had to do some thinking on our own. It was felt that there were reasonable grounds for disregarding the original alarmist calculations and since the Royal Air Force urgently wanted information on this as well as on aircraft contamination and decontamination we looked forward to the first British tests to supply the opportunity for getting details. Unfortunately, as you know, these were held at Montebello under conditions which could not be felt to give the R.A.F. any likelihood of getting reliable information and it was not until the Second Tests—October 1953—that we were given an opportunity of flying participation. We asked therefore for permission to carry out a detailed early study of just these points in relation to the Burst with a typical modern aircraft. The Air Staff were extremely co-operative and in early July 1953 we found ourselves the proud possessors of a brand new Canberra B2 with a really beautiful high speed finish on her to minimize the residual contamination hazard and to facilitate the decontamination procedures.

We removed the bomb sight and computers and installed special measuring and recording equipment which covered all rates of radiation that we might reasonably be expected to encounter from 0–10,000 r per hour. This consisted of two low-reading dose rate meters and two high-reading ones, all giving visual readings, the two higher rate ones also feeding on to spark-gap recorders so that we should have a graph of the levels throughout against a time scale and the known entry speed of the Canberra. As, however, the calculations that gave us these rates might be in error and as these rates were recognized to be dangerously high we had to devise a technique that would enable us to check the ionization peak before doing the complete cloud survey. We aimed to hit the cloud when the radiation had fallen to 5,000 r per hour or about 1.5 r per second—so we planned a tangential run on the cloud, enough to immerse the aircraft for about 2 seconds, when the exact rates could be seen and our calculations checked before the full run.

Film badges and electrosopes were carried by the crew to check the total integrated dosage as it was known that additional radiation would be received on the return journey from the outside contamination on the aircraft and from the collecting filters. A film camera was also used.

I will now let Wing Commander Geoffrey Dhenin describe the rest of the trip. Wing Commander Dhenin is Deputy Principal Medical Officer (Flying) of Bomber Command and the pilot of W.H.738—but before I finish I think I should say that the trip was a complete success and all data needed were obtained.

Wing Commander G. H. Dhenin:

Operation Hot-box

Bernard Shaw, once asked by a reporter what he thought of the feat of Amy Johnson in flying to Australia, replied that all the credit should be given to the aeroplane and that he could see little merit on her part since all she did was cling to the machine. In the operation which Group Captain Wilson is describing to-day my part was mainly that of limpet. The real work was done by the Group Captain, who originated the project and was a tower of strength, and by my navigator Wing Commander E. W. Anderson who had not merely to cling but to be intelligent about which way we were going or where we had just been, no mean task at 500 m.p.h.

The aeroplane, a new Canberra, W.H.738, was carefully prepared for the trip and its task. Various modifications were made to the fuel tanks, the navigation and radio equipment—these to simplify the task of flying a round trip of 20,000 miles, much of it over water. As to the task at

Woomera we tried to make a realistic estimate of the possible dangers we might encounter in the cloud and to do what we could to prepare for them. These risks were as follows:

- (1) The risk of hitting something solid in the cloud.
- (2) The risk of flameout due to the dust.
- (3) The risk of losing our airspeed indicator—again due to dust.
- (4) The risk of inhaling or swallowing radioactive dust.
- (5) The risk from external radiation.

The first risk we did not think very likely; but a high speed aircraft can be severely damaged by quite small objects, hailstones, for example. We had ejection seats to help us abandon ship if necessary and we saw to it that the seats were serviceable and that we were all familiar with the drills.

The second was also not very likely; but we had a special high energy system fitted to give us the best chance of relighting if the fires went out. If this proved impossible a good belly landing should present no difficulties in the open country where the explosion took place; and we later arranged for a R.A.A.F. Lincoln, piloted by a personal friend of mine, to stand by 50 miles away to locate us and drop supplies if we should crash.

The third risk was, I thought, quite a likely one; and though there should not be too much difficulty in landing without a knowledge of one's airspeed, a mistake can be very expensive. So we arranged for a R.A.A.F. aircraft to be airborne over Woomera for our return so that we could go in together in formation and he could call out to me the airspeed.

The fourth risk we countered by sealing the cabin—cutting off the pressurization air from the engines and sealing all possible leaks by fabric, dope and selotape. Though the cabin environment was scarcely enhanced by this treatment, we were, of course, using oxygen and preferred the discomforts of low pressure and no ventilation to the hazards of cabin contamination.

The fifth risk we could do little about except to calculate what radiation dose we could accept, and arrange to enter the cloud at a time appropriate to the dose.

With these arrangements settled we could prepare a plan for the operation itself. Here I will confine myself purely to the two factors which most affected the safety of the aircraft. The first of these was runway conditions. A strip had been prepared at X 200 and we were intended to operate from there. When we saw it, I felt that the loose surface might easily damage the aircraft and prejudice the success of the operation. Loose stones could be thrown up by the nose-wheel and engulfed by the engines with the most unpleasant results. We therefore decided to operate from Woomera, 300 miles away, not a great distance for an aircraft which can cruise at about 500 m.p.h.

Most important of all was the timing of the explosion. Since we wanted to be in a position to enter the cloud early we must not be too far away. On the other hand we must not risk exposing the aircraft to the actual explosion, nor must we be looking directly at it when it occurred. Apart from the normal danger of looking at atomic explosions, a blind pilot cannot regain control of an aircraft—and a Canberra once out of control hits the ground very fast indeed. We therefore planned our position in space very carefully; exactly three minutes before the explosion we should be ten miles from the site at a height of 30,000 feet on a course of 300° which would take us towards a dried-up salt lake with the melodious name Lake Meramangye. We should then—at this precise minute—start to descend at a fixed rate to bring us to the height at which we intended to meet the cloud. At H - 1 minute we were to get a check call from the airstrip at the explosion site (DUCK) and at H - 10 seconds we should begin an accurate turn (3°/sec.) towards the explosion. We should thus be turning towards the bomb but not far enough round the turn to see the flash directly. By the time we wanted to enter we should be at the right height, the right speed and very near the cloud.

This was the plan and we made numerous rehearsals, not only of the operation but of the details—starting up filter motors, ejection drills; getting out of the aircraft without picking up contamination, dropping the wing-tip filter and many other details. Finally after a long wait and many disappointments, we took off as dawn was breaking and set course for Emu. We reached it in a little over 40 minutes at 30,000 feet, but were dismayed to find that Lake Meramangye was no longer visible, partly because it was not a very clear morning and partly because some recent heavy rain had changed its appearance. We did our orbiting, therefore, using radio-compass bearings, and all went according to plan. We received the count-down properly and were partly round our turn, descending, when the flash came. I saw it only as a reflection from the cockpit canopy but it was quite bright enough. We completed the turn and started the run-up. As we levelled out I noticed that I was over-breathing hard. It occurred to me that of the two explanations for this—the high carbon-dioxide content in the cabin or fright—the latter was the more likely.

The first run was no more than a "sniff" as we called it—we just immersed our wings for a couple of seconds so that the Group Captain could tell us whether we could reasonably go through the middle. As I turned he made his calculations and decided that we could. I therefore headed the

aircraft straight at the centre and got ready for a rough ride. The cloud as we drew nearer, looked distinctly nasty. In colour it was a dark red-brown, very solid but boiling as it were. I turned on all the cockpit lighting, for it was certain that I should not be able to see my instruments without lights. As we entered, it was indeed dark but not as turbulent as I expected; until just before we emerged the forces on the elevators increased to such an extent that I thought I might lose control. Then, as the cloud gave us the parting kick, the light began to appear as at the end of a railway tunnel. We emerged, having hit nothing solid nor lost our engines or instruments. The rest was easy—a run through the base and the top, a quick beat-up of the scientists below, then back to Woomera to drop our wing-tip filter and leave the aircraft.

It was not yet 8 a.m. when we joined the circuit at Woomera where the Australian Canberra was airborne waiting for us. We had no need of his services, so we bade him good morning and went in to land. After landing we taxied to a dropping zone, established previously, to drop our wing-tip filter. This filter, now containing much highly radio-active material, lay in a wing-tip tank, secured to the wing by explosive bolts. When the wing was over the dropping zone, I jettisoned the tank which dropped cleanly on the sand; but it bounced, and being caught by the very strong wind began to roll towards the aircraft. There was nothing one could do but wait and hope that it would not damage any part of the machine. By good fortune it rolled under the nose, just clearing the nose wheel and was soon stopped by Dr. F. Morgan, the radio-chemist, who courageously turned the tank into wind and got some ropes on it to pull it back to the dropping zone where it was to lie and cool down for a week.

Meanwhile we taxied the aircraft to the area where we planned to decontaminate it, got out and cleaned ourselves in the coldest shower in the Southern hemisphere—an open shower fed by ice-cold water from a water cart while the wind blew at 30 m.p.h. and the sun was not yet up. Then we went to breakfast.

To return to what Bernard Shaw told the reporter, the aircraft cannot be praised too highly.

Despite the long distance it had covered, the penetration of an atomic cloud, the sundry disagreeable decontamination measures and what my pilot friends are pleased to call the supreme handicap of having a doctor to drive it, W.H.738 nevertheless broke the new record between Ceylon and Karachi on the way home.

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Section of Obstetrics and Gynæcology

President—FREDERICK W. ROQUES, M.D., M.Chir., F.R.C.S.Eng., F.R.C.O.G.

[October 22, 1954]

Pregnancy Complicated by Tumours

PRESIDENT'S ADDRESS

By FREDERICK W. ROQUES, M.D., M.Chir., F.R.C.S.Eng., F.R.C.O.G.

THE CASES

THROUGH the kindness of my colleagues and friends at Queen Charlotte's Hospital and Middlesex Hospital, and with the energetic assistance of my Registrar, Mr. Leonard Easton, I have been able to collect some 245 cases in which pregnancy was complicated by fibromyomata uteri and 63 in which it was complicated by ovarian tumours.

PART I

'PREGNANCY COMPLICATED BY FIBROMYOMATA

Of the 245 cases I found that there were 56 of no clinical significance. These comprised small symptomless tumours accidentally discovered during routine pre-natal or post-natal examination, which would not be expected to cause difficulties either during pregnancy or in labour. I think, therefore, it is not only justifiable but proper to subtract them, leaving 189 cases of pregnancy complicated by clinically important fibromyomata which were treated in the wards of Queen Charlotte's Hospital or the Middlesex Hospital, between January 1930 and July 1954.

THE RELATIONS OF FIBROMYOMATA WITH STERILITY

(1) It is, I think, generally agreed that fibroids are very much more common in women who are sterile. Whereas the general sterility rate is about 10%, the sterility rate in women with fibroids is about 30%.

Moreover, those sufferers from fibroids who are not sterile are very frequently infertile; the history in such cases is often one of an interval of five to twenty years since the last, and often the only, pregnancy.

Thus the tendency to produce fibroids is greater in the uterus which has not been allowed to fulfil its normal function; instead the abnormal results—a kind of perverted function.

It has been recognized for many years that the growth of fibroids is dependent upon ovarian activity; fibroids undergoing a diminution in size after the menopause, whether natural or radiologically induced, and after the operation of bilateral oophorectomy. The last fact has, of course, been known since the time when fibroids used to be treated by bilateral oophorectomy, before hysterectomy was made a safe operation by Sir John Bland-Sutton in the early part of the present century. No doubt the growth of the tumours is dependent upon one of the ovarian hormones, acting under the influence of the anterior lobe of the pituitary gland. Recent experimental work suggests that an excessive secretion of oestrogen can produce fibromata, and, in one instance, fibromyomata, in laboratory animals. Further, this experimental production of tumours can be inhibited by the simultaneous administration of progesterone.

Hadfield (1954) has shown in his work on the hormone-dependence of tumours that a cycle exists; the chain of events being the secretion of gonadotrophin from the anterior lobe of pituitary which evokes the secretion of oestrogen from the ovary—the *target organ*, as it is called; it is suggested that this oestrogen is utilized by the *responsive organ*, in this case the uterus, and the extent to which it is utilized determines the resulting blood-level of oestrogen. If the utilization by the responsive organ is high the resulting blood-level will be low; this results in further stimulation of the anterior pituitary to produce more gonadotrophin.

Since oestrogen appears to produce tumours in experimental animals it may be responsible for the development and growth of fibroids in the human female. Way (1954) states that fibroids are found in some 45% of feminizing ovarian tumours and co-exist with carcinoma corporis uteri in about 30% of cases. I believe the pharmacology of oestrogens also lends some support to this theory.

It may be that fibroids are common in sterile women because of continuous oestrogen stimulation unchecked and unopposed by the increased secretion of progesterone which occurs during pregnancy. But if this were so, then evidence of such continuous oestrogen stimulation would be present in all cases of fibroids. So far as I am aware such evidence is wanting.

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(2) Whether the presence of fibroids prevents or hinders conception is another and, therapeutically, more important question, upon which gynaecological opinion is divided, except in circumstances in which the tumours make conception impossible, namely (a) the fibroid polypus; (b) when the tumour or tumours make coitus difficult or impossible owing to situation and size; and (c) when salpingitis co-exists, as it does in some 10 to 12% of all cases of fibroids. In the presence of the last-mentioned complication the pathology may well be salpingitis, sterility, fibroids, in that order.

Giles (1919) denied that the presence of a fibroid could prevent conception, except in those three circumstances. Beckwith Whitehouse held a similar view. On the other hand Bonney's opinion (1935) was diametrically opposite.

To solve the problem statistically it would be necessary to know the general incidence of fibroids among women, the incidence of pregnancy in those who were known to have fibroids before marriage and the incidence of pregnancy in those who were known not to have had them before marriage. In these days when women frequently marry in the late thirties or early forties what answer are we to give to a patient aged 40, married for two years, coming to us with a fibroid as large as a hen's egg and wanting a family? My answer would be to remove the fibroid. Conception usually follows within the year. Regrettably this is an opinion which is not founded on statistical evidence: the number of cases I have collected is so small that I do not venture to quote them.

THE EFFECTS OF PREGNANCY ON FIBROMYOMATA

Certain changes commonly occur to fibroids during pregnancy. First, a change in position and, secondly, pathological changes.

(1) *A change in position.*—Fibroids accompany the uterus in its upward growth throughout pregnancy. That is axiomatic. The clinical importance is that fibroids situated in the lower uterine segment before conception almost always ascend into the abdomen afterwards. They rarely remain in the pelvis. It might reasonably be thought that cervical fibroids cannot make the ascent; but among the 189 cases there are 6 in which a single fibroid was situated in the cervix. In 2 of these delivery was normal. So it would appear that cervical fibroids can rise up and leave the pelvis free from obstruction. Mayhap, the fibroids were not truly cervical in these 2 cases.

(2) *Pathological changes.*—Pregnancy causes several pathological changes in fibroids, the two commonest being oedema and necrobiosis.

A. *Oedema.*—(Edema, due to increased vascularity, leads to a slight increase in size which is probably augmented by slight hypertrophy; it also causes the tumours to become softer and, often, flatter. The two last-named changes may make them more difficult to feel.

B. *Necrobiosis.*—Red degeneration is now generally believed to be due to hyaline degeneration in the walls of the blood vessels supplying the tumour; the weakened walls rupture with a resulting extravasation of blood. The sequential hæmolysis gives the tumour its characteristic red appearance. It is possible to see the red blood corpuscles under the microscope in necrobiosis, provided the sections are cut soon enough after the occurrence of the degenerative change and before their hæmolysis is complete. Necrobiosis is particularly liable to occur during pregnancy. Prof. F. J. Browne had an incidence of 17.3% in a series of 121 cases. In the present series of 189 cases necrobiosis occurred in 30, or 15.8%.

The fibromyomata were intramural in 22 of the 30 cases and of the pedunculated subserous type in 8. Among the total of 189 cases the fibroids were intramural in 160 and pedunculated subserous in 29.

TABLE I.—FIBROMYOMATA COMPLICATING PREGNANCY

Type of fibromyoma	Cases	Necrobiosis	Per cent
Intramural	160	22	13.75
Pedunculated subserous	29	8	27.6
Total	189	30	15.8

Though the figures are too small to be conclusive, these findings are unexpected and unusual. as red degeneration is said to be more common in intramural fibromyomata than in the other varieties, and that is certainly my own experience.

THE EFFECTS OF FIBROMYOMATA ON PREGNANCY, LABOUR AND THE PUERPERIUM

(1) *Pregnancy.*—As is well known the incidence of pregnancy in association with fibromyomata is small; according to Spencer (1920) pregnancy is complicated by fibromyomata in 0.6% of cases: Monro Kerr and Chassar Moir found the incidence to be 0.8%. In the present series from 1930 to 1954, out of a total of 69,656 deliveries there were 245 fibromyomata, or approximately 0.35%.

In this connexion I think it is justifiable to include the 56 cases with clinically insignificant tumours. The incidence appears to be lower than the average; but if the cases reported before 1946 are excluded—when case records were not so well tabulated as they are today—then a figure more approaching that of Spencer's is obtained.

TABLE II.—PREGNANCY COMPLICATED BY FIBROMYOMATA, INCIDENCE

Years	Total deliveries	Fibromyomata	Per cent
1930 to 1946	38,629	41	0.11
1946 to 1954	31,027	204	0.65

Whichever figures are accepted the incidence is admittedly low; but although low, it is sufficiently high for an appreciable number of cases to be seen in a busy maternity department during the course of a year and it behoves us briefly to review the possible complications in pregnancy and the difficulties during labour caused by the concomitant presence of fibroids in the uterus.

Miscarriage may be caused; it is, of course, most likely to occur when the situation of the tumour is submucous, least likely when the only fibroid present is subserous and pedunculated. In the present series of cases miscarriage occurred in 9 out of 189, an incidence of 4.8%.

In one of these cases miscarriage followed myomectomy before viability; the other 8 occurred in the absence of any operative interference.

This is a very low figure when compared with that of some other authors. Browne, for instance, had 29 cases of miscarriage in his series of 121, or 23.9%; and Gemmell (1936) 13.6% in 475 cases. I am at a loss to explain the discrepancy, although it must not be forgotten that many of the cases come from Queen Charlotte's Hospital, where miscarriage is not treated. I shall later have occasion again to refer to these figures.

The duration of the pregnancy at the time of miscarriage and the situation of the fibromyomata are shown in Table III.

TABLE III.—PREGNANCY COMPLICATED BY FIBROMYOMATA
Miscarriage 9 cases

Duration of pregnancy in weeks	Cases	Situation of fibromyomata	Cases
12	3	Submucous	2
14	2	Intramural	6
16	1	Unknown	1
20	2		
26	1		

Other complications.—A fibroid, particularly if situated in the posterior uterine wall, may cause retroversion of the pregnant uterus; sometimes incarceration with retention of urine will result.

Fibroids, by interfering with the engagement of the head in the pelvis, may produce malpresentations.

(2) *Labour.*—(i) *Premature labour* (Table IV):

TABLE IV.—LABOUR COMPLICATED BY
FIBROMYOMATA
Labour Before the Fortieth Week of Gestation
6 cases

Duration of the pregnancy in weeks at onset of labour	Cases
27	1
32	2
36	1
38	2

TABLE V.—LABOUR COMPLICATED BY
FIBROMYOMATA
Delivery per Vias Naturales
36 cases

Forceps delivery because of delay in the 2nd stage ..	24
Forceps delivery because of foetal distress ..	7
Total forceps delivery ..	31 or 86%
General forceps rate at the two hospitals ..	13.5%

The child delivered at the 27th week died shortly after spontaneous delivery. One of the children delivered at the 32nd week died *in utero* before delivery, death being due to chorionitis. The other delivered at the 32nd week died shortly after delivery. The last case was further complicated by post-partum hæmorrhage and manual removal of the placenta.

(ii) *Labour at term:* Out of the 189 cases, then, miscarriage occurred in 9, leaving 180 cases. Of these 180 cases delivery *per vias naturales* occurred in 36.

These figures in Table V, although small, indicate that the presence of fibromyomata considerably increases the necessity for forceps delivery. This is to be expected because of interference with the uterine contractions. The indications for the use of the forceps are shown in Table V.

(iii) *Obstructed delivery:* The second stage of labour can be complicated by a tumour lying in the pelvis and causing obstruction to natural delivery. This is usually diagnosed before labour and treated by Cæsarean section. In this series Cæsarean section was undertaken for obstruction during labour in only 4 cases.

(iv) *Post-partum hæmorrhage:* The third stage may be complicated by post-partum hæmorrhage, especially with submucous tumours; and particularly if the placental site covers the surface of a submucous tumour. In the present series of 36 cases, in which delivery was *per vias naturales*, post-partum hæmorrhage occurred in 16 or 44.4%. This is a very high figure when compared with the average incidence of post-partum hæmorrhage, about 10%.

Moreover manual removal of the placenta was necessitated in 11 cases, or 30.5%. In 3 of these it is recorded in the case-notes that the placenta was adherent to the surface of a submucous tumour.

(3) *The puerperium*.—The chief puerperal complication is, I suppose, infection of a submucous tumour or polypus; torsion of the pedicle may occur with pedunculated subserous growths and the extrusion of a polypoidal submucous fibroid has been recorded. Lockyer recorded a case in which a fibroid polypus was extruded between the delivery of the child and that of the placenta. None of these complications occurred among the cases here reported.

Diagnosis.—It is not usually difficult to diagnose fibroids early in pregnancy; the earlier the easier; the later, the more difficult the diagnosis becomes. This applies especially to a tumour in the posterior uterine wall which cannot possibly be felt during the later months of gestation. A fibroid in the lower uterine segment has been mistaken for placenta prævia on radiological examination.

TREATMENT

When fibromyomata are diagnosed in the early months of pregnancy two alternative methods of treatment are available:

Operative treatment, in this connexion, implies the removal of the fibroids by myomectomy before the child is viable.

Conservative treatment implies surgical inactivity until shortly before term when delivery may either be *per vias naturales*, or by Cæsarean section. If this operation is performed the fibroids may be left in situ, or they may be removed by myomectomy, or treated by hysterectomy.

Among gynaecologists I have no doubt that the almost universal attitude upon this question is one of conservatism. The arguments in its favour are, briefly, five:

First, many women with fibromyomata pass through pregnancy without difficulty. It is true that necrobiosis occurs in an appreciable number of cases; in nearly 16% of the present series. But necrobiosis, although painful, is not a dangerous condition; it almost always responds to the conservative measures of rest in bed and the exhibition of sedative and analgesic drugs, particularly morphia, within seven to fourteen days.

Secondly, patients with fibroids are relatively infertile and operation frequently involves risking the patient's only opportunity of motherhood.

In this series out of 189 cases, 155 patients, or 82%, were pregnant for the first time.

Thirdly, operative interference may be followed by abortion; as it was in 1 out of the 13 cases treated by myomectomy before viability.

Fourthly, although the abdomen may be opened with the intention of performing myomectomy the local conditions may be such as to demand hysterectomy; or myomectomy may be possible only after removal of the products of conception.

Fifthly, the morbidity and mortality risks of myomectomy are undoubtedly increased by the co-existence of pregnancy. The fibroids are less easily removed because the plane of cleavage between the tumours and their capsules is less well defined; hæmorrhage is more profuse and more difficult to control.

Evidently those responsible for the treatment of the 189 cases reported here favour conservative treatment during pregnancy, as shown in Table VI.

TABLE VI.—PREGNANCY COMPLICATED BY FIBROMYOMATA
Operative treatment before viability. 19 Cases

Operation	Number of cases	
Myomectomy followed by normal delivery	11	57.9%
Myomectomy followed by miscarriage	1	42.1%
Myomectomy with removal of the products of conception ..	1	
Hysterectomy	6	

These are telling figures, showing the loss of close upon half the children. They lend strong support to my fourth reason for animadverting upon operative treatment early in pregnancy, namely, although the abdomen may be opened with the good intention of performing myomectomy the local conditions may necessitate either hysterectomy or myomectomy only after the removal of the products of conception. Attempted myomectomy during pregnancy may lead to having to sacrifice the child. Add to that the fact that more than 80% of the mothers were pregnant for the first time. If we accept these figures, we have ample reason for folding our surgical hands until term approaches. Here is a time for *masterly inactivity*, coupled, as always, with *watchful expectancy*.

Vaginal delivery following myomectomy.—Natural delivery at term followed myomectomy, performed during the earlier weeks of pregnancy, in 11 cases. This is interesting because the fear of rupture of a scar in the uterus sometimes prompts the surgeon to advise Cæsarean section in cases in which myomectomy has been undertaken during pregnancy.

Fœtal mortality.—Myomectomy has been advocated during pregnancy because of the fœtal mortality if the fibroids are left in situ; Pierson (1927), in analysing 250 cases of fibroids among 30,836 pregnancies, found the fœtal mortality from all causes to be 32.1%, contrasting with a fœtal mortality of 6% in a series of unselected cases. Browne had a stillbirth-rate of 28.8% in his series of 121 cases, while Gemmell's total fœtal loss was 38.7%.

My figures are somewhat lower. The total number of children lost was 23. The causes are shown in Table VII.

TABLE VII.—PREGNANCY COMPLICATED BY FIBROMYOMATA. 189 CASES

Loss of children 23 cases										Number of cases
Cause										
Miscarriage	8
Miscarriage following myomectomy before viability	1
Hysterectomy before viability	6
Myomectomy before viability with removal of the products of conception	1
Stillbirth following natural delivery	3
Stillbirth following Cæsarean section	1
Neonatal death following premature labour	3
Total										23 or 12.1% loss of children

These cases can be divided into three groups:

- (1) Those in which operation was performed before viability.
- (2) Those in which no operation was performed.
- (3) Those in which operation was performed about term.

In the first group there were 8 foetal deaths; 6 in which hysterectomy was undertaken before viability, one in which the uterine contents were evacuated to facilitate myomectomy and one in which miscarriage followed myomectomy. The total number of patients in this group was 19. So that the foetal loss in this group was about 42%.

In the second group the foetal and neonatal death-rate, including the 8 cases of miscarriage, was 14 out of a total of 45 or about 31%.

In the third group there was one stillbirth out of 125 cases treated by operation about term; a foetal mortality of approximately 0.8%.

These figures do not lend support to the view that myomectomy during the early months of pregnancy reduces the foetal and infantile loss. Indeed the loss was greatest among the patients treated by operation before viability.

CONSERVATIVE TREATMENT

When the diagnosis is made early an expectant line of treatment is wisest. The pregnancy should be carefully supervised and a watch kept for untoward symptoms. Threatened miscarriage, as evidenced by vaginal bleeding, should be conservatively treated on orthodox lines and necrobiosis should be similarly treated. There are a few very rare complications which must be treated by laparotomy, such as intraperitoneal hæmorrhage, torsion of the pedicle of a pedunculated fibroid, torsion of the pregnant uterus and incarceration of a retroverted pregnant uterus containing a fibroid which cannot be replaced under anaesthesia after catheterization of the bladder. But these are all rarities.

Sooner or later, preferably sooner, before term the important decision as to the method of delivery will have to be made. First, whether it is to be vaginal or abdominal; and, secondly, if abdominal whether myomectomy or hysterectomy should be combined with the Cæsarean operation.

In cases in which a fibroid is situated in the pelvis and will obstruct delivery Cæsarean section is imperative and should be performed shortly before term. This operation was necessitated in 4 of our cases.

In other cases it is difficult to specify which patient should be allowed to deliver herself normally and which should be treated by Cæsarean section. Natural delivery would be chosen in the case of a single small fibroid situated in the upper uterine segment; while in the case of fifty tumours Cæsarean section with hysterectomy would be the practice of most of us. But the majority of cases lie between these two extremes and each must be judged on its own merits. There are, however, certain considerations which should be borne in mind when making a decision on this important question.

First, while admitting that pregnancy is often uneventful in the presence of fibroids, it must not be forgotten that complications, sometimes serious complications, especially during labour, can and do occur.

Secondly, failure of the head to engage in the pelvis before the onset of labour in a primigravida, or a malpresentation, would weigh the scales in favour of abdominal delivery.

Thirdly, the parity of the patient has an important bearing on the question. Often the pregnancy is the first as it was in 82% of this series; the patient rarely has more than one other child. Here is another factor influencing the decision in the direction of Cæsarean section.

Fourthly, the age of the patient must always be taken into account. Nearly always the patients are of an age when the prospects of child-bearing are diminishing in arithmetical progression.

TABLE VIII.—PREGNANCY COMPLICATED BY FIBROMYOMATA
Age incidence. 245 Cases

Age in years	Number of cases	
	Group I	Group II (all cases)
19 to 29	36	54
30 to 39	122	156
40 to 46	31	35
Total cases	189	245
Average age	35.4	36.4

Table VIII shows the ages of the patients. Group I comprising the 189 cases in which the fibroids were clinically significant, and Group II in which some of the fibroids were of no clinical significance.

The youngest patient was 19 and the oldest 46 years of age.

Fifthly, the duration of married life prior to the onset of the existing pregnancy is a factor which is sometimes neglected. None the less it is important.

Sixthly, the presence of a complicating disease, such as pre-eclampsia; or an obstetric complication, such as placenta prævia; or some associated disease, such as cardiac disease, may have to be given consideration.

Seventhly, the size, position and number of tumours present. The greater the number and the larger the size the stronger is the indication for Cæsarean section with hysterectomy.

These seven points must be considered together. A combination of some two, three or more, forms a valid reason for Cæsarean section. We can all recall cases in which age, a long period of sterility following marriage and multiple fibromyomata have led us to advise Cæsarean section.

If the decision reached is to deliver the child *per abdomen* should the fibroids be dealt with at the same operation and if so by myomectomy or by hysterectomy? Cæsarean section with myomectomy is a procedure to be avoided as being fraught with very considerable risk owing to the torrential hæmorrhage which takes place from the cavities left after the enucleation of the fibromyomata; even after apparently complete closure and obliteration by mattress-sutures hæmorrhage often continues from the stitch-holes and suture line. In theory it should be possible to arrest the bleeding; in practice it is frequently impossible.

Myomectomy immediately after Cæsarean section is advisable only in the case of a pedunculated tumour, when the fibroids are of insignificant size, or few in number.

Cæsarean section with myomectomy was performed in 41 cases of the present series (Table IX), that is to say in nearly 26% of the conservatively treated cases.

TABLE IX.—PREGNANCY COMPLICATED BY FIBROMYOMATA

Cæsarean Section with Myomectomy.
41 Cases

Situation of fibroid	Number of cases	Blood transfusion required
Intramural	31	3
Pedunculated subserous	10	1
Total	41	4

TABLE X.—PREGNANCY COMPLICATED BY FIBROMYOMATA
Treatment. 180 Cases

		Per cent
Myomectomy during pregnancy	13	7.3
Hysterectomy before viability	6	3.3
Delivery <i>per vias naturales</i> at term	36	20
Cæsarean section	73	40.5
Cæsarean section with myomectomy	41	22.8
Cæsarean section with hysterectomy	11	6.1
Total	180	

The patients and their infants all survived, and the number of cases requiring transfusion was remarkably small.

These figures, small though they are, do not bear out my pessimistic attitude towards the combined operation of Cæsarean section and myomectomy. The cases were, no doubt, carefully selected and they were in good hands. For my own part I shall continue to regard the operation of Cæsarean section with myomectomy with awe. In those cases in which operative delivery has been decided upon but which are unsuitable for myomectomy there are only two alternatives: either to deliver the child by Cæsarean section, leaving the fibroids to be dealt with later, or to remove the uterus with its tumours. The most sensible course is to remove the uterus in those cases in which myomectomy would be impossible at a later date and to conserve it with its fibroids when there is a reasonable expectation of safely performing myomectomy after involution is complete and after an interval of six months. Certainly it would be ill-advised to attempt it with an interval of less than three months.

I shall now briefly review the treatment followed in my group of 180 cases after deducting the 9 miscarriages (Table X).

There was one maternal death among the 73 cases of Cæsarean section without hysterectomy. Apparently the patient died of uncontrollable post-partum hæmorrhage in spite of several blood transfusions. There was also one foetal death, from asphyxia, in these cases.

Cæsarean section was undertaken in 73 out of 84 cases without surgical treatment of the fibroids. I am amazed at the large number of cases in which the fibroids were left and at the small number in which hysterectomy was combined with the Cæsarean operation.

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PART II

PREGNANCY COMPLICATED BY OVARIAN TUMOURS

Incidence.—Ovarian tumours are uncommon in association with pregnancy, the incidence usually being quoted as 1 in 1,500 cases. The present 63 cases (Table XI) occurred among approximately 70,000 deliveries, an incidence of 0.09% or somewhat less than 1 in 1,000.

TABLE XI.—OVARIAN TUMOURS COMPLICATING PREGNANCY
63 Cases

	Cases	Percentage
Dermoid cysts	24	38.1
Simple serous cysts	22	47.6
Fimbrial cyst	1	
Broad ligament cyst	2	
Corpus luteum cysts	5	
Pseudomucinous cysts	6	9.5
Papillary cystadenoma	1	4.8
Ovarian fibroma	1	
Chocolate cyst	1	

Type of tumour.—The commonest ovarian tumours are simple unilocular or multilocular cysts and dermoid cysts. The relative incidence of the former is about 60 to 70% and of the latter 20 to 25%. The present cases broadly conform to these figures as can be seen in Table XI.

THE EFFECTS OF PREGNANCY ON OVARIAN TUMOURS

In about 12% of pregnant cases torsion of the pedicle of an ovarian tumour occurs, while the incidence is about 8% in non-pregnant patients.

Rupture of the cyst, intracystic hæmorrhage, infection and necrosis can occur but are not, I think, any commoner among pregnant than among non-pregnant patients. Injury and necrosis may result from pressure on the tumour during labour. During the puerperium the pedicle is liable to become twisted owing to the rapid decrease in the size of the uterus; the laxity of the abdominal walls after delivery may be another factor predisposing to torsion. Infection and suppuration also occasionally occur.

Torsion of the pedicle occurred in 2 of the 63 cases; in one at the fifteenth week of gestation, and in the other seven days after spontaneous delivery at term. Both patients were treated by ovariectomy. The former was subsequently normally delivered at full time.

Rupture of the cyst occurred in 2 cases. In both the rupture was found during a planned laparotomy on the twelfth day of the puerperium; in both cases delivery had been assisted by forceps.

THE EFFECTS OF OVARIAN TUMOURS ON PREGNANCY

Usually pregnancy continues undisturbed by an ovarian tumour but miscarriage may be produced by interference with uterine growth.

Labour will be obstructed by a tumour situated in the pelvis; obstruction is relatively more common than with fibromyomata which nearly always ascend into the abdomen before it begins.

There is no instance of miscarriage in the 14 cases of this series in which operation was not undertaken until after delivery.

In 11 cases the cysts were intrapelvic and offered obstruction to natural delivery; in 6 of these the diagnosis was made during labour.

Diagnosis.—It is easier to diagnose an ovarian tumour early than late in pregnancy. A full bladder has been mistaken for an ovarian cyst!

TREATMENT

An ovarian tumour should be removed as soon as it is diagnosed whether the patient is pregnant or not. It may be malignant or it may become malignant. Moreover while the tumour remains in the peritoneal cavity it is subject to the risks of torsion of the pedicle, rupture, intracystic hæmorrhage and other secondary changes.

When pregnancy co-exists an ovarian tumour should always be removed if diagnosed during the first half of gestation; indeed I should advise removal up to the 32nd week, for the reason that the tumour is potentially, if not actually, malignant. When the diagnosis is made in the very early weeks it is preferable to delay operation until after the 14th week because the danger of miscarriage is then less than it is during the first 12 weeks.

When the diagnosis is not made until late in the pregnancy, either Cæsarean section with ovariectomy should be carried out shortly before term; or natural delivery at term and ovariectomy during the puerperium. With an intrapelvic tumour which will obstruct delivery the former method will be selected; in those in which it is not offering obstruction the latter may be the treatment of choice.

The treatment in the 63 cases is shown in Table XII.

In 33 of these the ovary was removed with its contained cyst—ovariectomy; in the remaining 30 the

cyst was excised from the ovary—the so-called ovarian cystectomy. The ovarian cystectomyes were all performed after 1939.

The cyst was removed during pregnancy in 29 cases, in the puerperium in 14, while the combined operation was undertaken in 20 (Table XII).

TABLE XII.—PREGNANCY COMPLICATED BY OVARIAN TUMOURS. 63 Cases					
Method of treatment	Cases	Miscarriage	Neonatal death	Age	Cases
Ovariectomy before the 20th week	21	1		20 to 29	21
" after 20th week	8	1	1	30 to 39	27
" after natural delivery	14				
Cæsarean section with ovariectomy	20				
Total	63	2	1	Average age	29.9 years.

Operation was performed before the 20th week in 21 cases and after that date in 8 cases. Miscarriage followed operation in 2 cases, one in each group; the one in the second group of 8 cases, followed the removal of a chocolate cyst at the 26th week.

The neonatal death followed forceps delivery at the 38th week. A large ovarian cyst had been removed through a short abdominal incision after the aspiration of 22 pints of fluid two days previously. This strikes me as a remarkably sensible operation in the case of a very large cyst diagnosed very late in pregnancy; although I think I should prefer to remove the child by Cæsarean section and then remove the cyst, at the same time through a long incision.

Removal of the cyst was combined with Cæsarean section in 20 cases (Table XII) with survival of all the mothers and infants.

In 11 cases the cyst was situated in the true pelvis; in 6 it actually, and in 5 potentially, offered obstruction to delivery: that is to say that in 6 of the 11 cases the diagnosis was made and operation undertaken during labour.

In these 11 cases, 5 diagnosed late in pregnancy and 6 during labour, there was no alternative to the combined operation; because few of us care for our patients to face labour with a recently healed abdominal wound.

Subtracting the 11 cases from the 20 we are left with 9 in which it was evidently thought advisable to deliver the child abdominally, although vaginal delivery would not have been obstructed. The question of the treatment of these cases, diagnosed late in pregnancy, in which obstruction to delivery is not offered, is one in which there is some divergence of opinion. The disadvantage is, of course, that Cæsarean section leaves a scar in the uterus which may rupture during a subsequent labour; this disadvantage is accentuated by the fact that the patients are often young women who are likely to bear more children.

The youngest patient was aged 20, the oldest 38 years; the majority being in the twenties.

The probability of future pregnancies is enhanced by the additional fact that primiparity seems to be common in these cases, as would be expected in view of the age-incidence. The pregnancy was the first in 58 out of the 63 cases at present under consideration.

If these arguments hold, then the case for vaginal delivery with removal of the ovarian cyst during the puerperium is won. Cysts not so situated as to obstruct delivery *per vias naturales*, or not of such enormous proportions as to hinder such delivery, should be removed during the puerperium.

However, there is something to be said for the combined operation of Cæsarean section and ovariectomy even in cases in which the cyst will not obstruct vaginal delivery, because labour does not spell the end of our troubles. On the contrary labour may be the cause of rupture; it appears so to have been in 2 of the cases discussed here; while torsion of the pedicle is a well-recognized puerperal complication, as it was in one of our cases.

When we are called upon to deal with an ovarian cyst, which is not likely to obstruct delivery and diagnosed late in pregnancy, we should deal with both at the same time, thereby avoiding parturitional and post-parturitional complications; above all being merciful to our patient by saving her the agonies of labour so soon to be followed by an abdominal operation. But the answer really depends upon how one regards a scar in the uterus. It is not my intention to enter into either the causes or statistics regarding uterine rupture following Cæsarean section; but, for my own part, I think the danger of rupture during subsequent labour has been exaggerated. It is really very small.

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Section of Comparative Medicine

President—Sir WELDON DALRYMPLE-CHAMPNEYS, Bart., M.A., D.M., F.R.C.P.

[October 20, 1954]

Non-Specific Physiological Factors Controlling the Phenomena of Parasitism

PRESIDENT'S ADDRESS

By Sir WELDON DALRYMPLE-CHAMPNEYS, Bart., M.A., D.M., F.R.C.P.

It has seemed to me that to explain the phenomena of infectious disease in terms of micro-organisms, protective antibodies and phagocytes was as inadequate and unfruitful as to account for falling in love in photographic terms. In saying this I am not neglecting the original experiments and inspired deductions of such great men as Koch, Pasteur and many others in elucidating the specific defences possessed by the individual, either from inheritance or by personal experience of the pathogen concerned, but we should not forget that Pasteur's wide ranging gaze was never confined within this narrow field. "If", he wrote, "you place under good conditions of nutrition and of climate this child born of tuberculous parents, you have a good chance to save him from tuberculosis . . . There exists, I repeat it, a fundamental difference between the disease itself and its predisposing causes." As regards the phagocytes, these do not always fight on the side of the host, but often afford protection from antibodies and drugs to the ingested parasitic cells, a function in which many pathologists believed before Metchnikoff, as Cameron (1952) has pointed out. (Miles has, however, suggested that the phagocytes may help defence by aiding dispersion of the ingested parasites to a portion of the reticulo-endothelial system where they can be dealt with more effectively.)

For many years now I have asked repeatedly "Why if I lie out all night in the snow am I likely to develop pneumonia? What is the fundamental mechanism of this so-called 'lowering of resistance' about which people talk so glibly?" but no answer could I get. (I shall refer later to the anomalous results of chilling obtained in investigations of the common cold.)

But if the benefits derived in the last seventy years from actively provoking the formation of specific antibodies against particular infections have been enormous, how much greater might be expected to be the benefits of assisting those fundamental mechanisms which constitute an important, I believe the most important, defence of the body against the attacks, whether by open invasion or fifth column methods of innumerable species of pathogenic micro-organisms?

The problem I propose to consider will be made all the clearer by appropriate illustration and I will give as my first illustration the behaviour of *Brucella* in the human body, behaviour which in many ways closely resembles that of *M. tuberculosis*.

Like everyone else who has investigated the behaviour of the genus *Brucella* I have been struck by the extraordinary variation in the results of parasitism by this organism. As regards invasion the great majority of persons consuming a milk supply infected with *Brucella* (the usual source of infection in the country) do not become infected. When invasion occurs some persons presumably overcome the invaders completely, others are not so successful, but establish a comfortable symbiosis, usually with the development of specific allergy demonstrable by the intradermal test with brucellin. In some patients this allergy may give rise to symptoms referable to the nervous, gastro-intestinal,

respiratory and other systems, this being the condition often described as "chronic brucellosis". In other patients a definite acute illness follows invasion and this illness may either clear up completely, though *Brucella* often persists in the body, or may subside into the chronic form of the disease.

In some cases, however, of which I have had several dozen, undulant fever of the acute type continues over a period of years (in one case forty-three years), with occasional intermissions followed by the return in full force of the former symptoms.

Now it is important to note firstly that from time to time a patient no longer presenting signs of the acute disease, whether he is clinically well or suffering from the chronic form of the disease, may, presumably as the result of the disruption of a local focus of infection due to changes in the body which are usually quite obscure, suffer from a febrile episode; and secondly that the wide differences in behaviour following invasion by *Brucella* are not accompanied by corresponding variations in the titre of any specific antibodies so far identified—agglutinins, opsonins, bactericidal antibodies¹, &c.—any more than the severity of the acute disease or its prognosis is correlated with the quantities of such antibodies present in the blood. That such differences in response are not due to variations in the virulence of the infecting organism is suggested by Spink and Anderson's (1954) recent demonstration that *Brucella* endotoxins, from smooth cultures of many different strains of *Brucella*, possess the same degree of lethal power in mice and that differences in the clinical results of infection with, say, *Br. abortus* and *Br. meli* respectively are probably due to differences in the facility with which the organism multiplies in the body. This explanation receives support from recent work (Pierce *et al.*, 1953; Pierce and Middlebrook, 1947; Suter and Dubos, 1951) with mammalian tubercle bacilli which has revealed a striking correlation between virulence (ability to produce lesions or cause death in guinea-pigs and mice) and the initial rate and extent of multiplication of the various mammalian strains in the organs of mice. On the other hand the environment can change the antigenic structure of the invading organism. Thus *Brucella* grown in media in which alanine is allowed to accumulate tends to change from the S to the R colonial type. This change requires the presence of Mn⁺⁺ ions and is inhibited by the presence in the medium of chelating agents which bind this cation (Dubos, 1954b). It is also under the control of some serum constituents, the concentration of which varies from one species of animal to another and with the state of disease or of immunity (Braun, 1952).

Now does not this whole brucellosis picture carry conviction that, in this disease at least, the non-specific host factors are of paramount importance in determining the phenomena which result from parasitism?

But lest it be thought that such an argument is only applicable to this particular genus let us look at the tubercle bacillus which resembles *Brucella* in much of its behaviour. Writing of the downward trend in tuberculosis mortality in this country and in the United States which began soon after 1850, Dubos remarks, quite justly in my view, "Neither the discovery of the tubercle bacillus nor the growth of the sanatorium movement, nor the organization of the anti-tuberculosis associations, nor the introduction of pneumothorax therapy, seem to have affected markedly the shape of the mortality curve. As to thoracic surgery, vaccination with BCG, antimicrobial treatment with streptomycin and PAS, they are of such recent origin, or have been used on such limited scale, that they could not have played any part in the phenomena under discussion" (Dubos, 1951). Has the progressive decrease in prevalence and severity of the disease been due, then, to reduced pathogenicity of the tubercle bacillus for man? Neither experiments in animals nor the violence of its effect upon a virgin population supports this view. It would seem, therefore, that man has become more resistant to this pathogen and here various factors may be involved, inherited resistance and the natural elimination by the disease of susceptible families, the cumulative reduction of the number of persons exposed as the number of open cases is reduced, immunization by abortive contact infections, &c. But immunity from an aborted infection is only relative and is frequently broken down when a population is exposed to unfavourable living conditions, as happened so often in the two World Wars. Though we are all familiar with the effects of overcrowding, under-nourishment, bad ventilation, lack of sunlight, &c., on the tuberculosis death-rate, we know practically nothing of the mechanism at work inside the body, and even the most effective anti-tuberculosis campaigns have not succeeded in preventing infection of the great majority of the populations of most countries, as revealed by the skin sensitivity tests. It is in fact still very difficult to account for the lagging of morbidity rates behind mortality rates. There is some evidence that diet plays a part here, as was shown by the reversal for a time during World War I of the downward curve of tuberculosis mortality in Denmark, probably in consequence of the enormously increased export of meat and dairy products to England between 1915 and 1917; and the reduced mortality in Normandy and Brittany in World War II when exchange difficulties interfered with the transport of the same products to other parts of France so that more was consumed locally. But we do not know in the least what food components were important here, or what was the mechanism involved and, as I shall show presently, abundant nutrition does not always spell increased resistance to disease, for sometimes the reverse is true.

One of the classical and most powerful means in the past for halting the progress of tuberculosis in the individual has been rest, but what do we know of the way in which this acts? Is it by promoting

¹ Hall (1950) has described a specific bactericidin-inhibitor which may exert an action in chronic *Br. cel* infections.

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healing of diseased tissues and if so how? or does it act by preventing spread to new sites? As every tuberculosis physician knows, the rest required is not only mechanical but also physiological and psychological.

Another indicator of the importance of general physiological factors in resistance to tuberculosis is given by the age incidence of the disease, which reveals that between the ages of 5 and 15, which has been termed "the golden age of tuberculosis", children suffer a much lower incidence of the disease than in the younger and older groups, nor is the relatively high resistance to disease in this age group peculiar to tuberculosis but, as Dubos (1951) has shown in the United States in the years 1900 and 1940, it was shared by "pneumonia and bronchitis", and also by the ill-defined group labelled "diarrhoea and enteritis". It is certainly interesting that this variation of susceptibility to infection with age was as evident in 1900, when infection was nearly universal, as it was in 1940, with a very different general prevalence.

The mortality rates for England and Wales for the same two years for pulmonary tuberculosis and for pneumonia (all kinds) show the same advantage for children aged 5-15, and this applies to both sexes.

TABLE I.—MORTALITY RATES OF TUBERCULOSIS, PNEUMONIA AND BRONCHITIS, DIARRHOEA AND ENTERITIS BY AGE GROUPS IN THE UNITED STATES IN 1900 AND 1940 (DUBOS, 1951)

Age group	1900			1940		
	Tuberculosis	Pneumonia and bronchitis	Diarrhoea and enteritis	Tuberculosis	Pneumonia and bronchitis	Diarrhoea and enteritis
5	146.1	862.7	1175.1	14.6	188.4	102.4
5-14	36.2	39.7	8.8	5.5	6.9	0.9
15-24	205.7	47.1	5.7	38.2	8.8	0.7
25-34	294.3	74.4	7.5	56.3	13.4	1.0
35-44	253.6	109.2	1.05	59.4	22.8	1.6
45-54	215.6	169.3	18.6	66.3	42.9	1.9
55-64	223.0	331.2	49.3	76.1	83.0	3.4
65-74	256.1	683.1	130.4	80.8	187.4	7.0
75+	269.2	1666.7	365.8	77.8	691.8	29.8

TABLE II.—MEAN ANNUAL MORTALITY PER MILLION LIVING, ENGLAND AND WALES

Age years	Phthisis				Pneumonia*			
	1900		1940		1900		1940	
	Males	Females	Males	Females	Males	Females	Males	Females
0-					14,738	10,895	11,674	8,817
1-	350	298	50	55	3,790	3,400	1,234	1,038
5-	131	198	23	24	228	211	82	75
10-	184	417	42	100				
15-	876	1,059	398	725	381	181	124	65
20-	1,908	1,465	1,419	1,060				
25-	2,355	1,811	969	758	696	324	178	109
35-	3,273	2,088	1,000	517	1,409	587	314	166
45-	3,440	1,593	1,213	354	2,100	872	736	317
55-	2,838	1,216	1,288	319	2,974	1,539	1,456	656
65-	1,557	840	725	263	4,119	2,611	2,305	1,612
75 and over	591	373	262	137	5,085	4,152	4,990	4,322

*All forms (lobar, broncho—and unspecified).

A similar resistance to infection, but starting earlier, is shown by the age distribution of my cases of undulant fever, in spite of the fact that it is at this age that milk, the usual vehicle of infection in this country, is most prominent in the diet.

TABLE III.—AGE DISTRIBUTION OF 1,194 CASES OF UNDULANT FEVER

Age group	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65 and over
Males	7	36	26	57	46	78	96	85	91	73	71	41	31	29
Females	4	18	21	24	26	26	41	44	41	41	41	27	41	32
Total	11	54	47	81	72	104	137	129	132	114	112	68	72	61

The age incidence of infectious disease has not, I think, received the attention it deserved (the localization of infection and of skin rashes are other instances of this neglect), perhaps because of its familiarity, and when it has been considered too much emphasis has been placed on the effect of specific immunity both inherited and acquired. That other factors are important here is shown in the case of the common cold.

I think most physicians would agree that in later life the common cold is less common (Dingle and his co-workers (1949), showed that in urban populations children had nearly twice as many colds as adults, but the evidence seems to be on the whole against the acquisition of immunity to the virus of the common cold or, if immunity does result from an attack it must be very short lived (Andrewes, 1950;

Pollard and Caplovitz, 1948). I may remark here that though in *Brucella* infection the existence or absence of true immunity is very difficult to determine owing to the lurking habits of the organism, it is certain that a patient who has apparently completely recovered from a severe attack of undulant fever, may, nevertheless, develop an exactly similar illness after a longer or shorter interval, whether as the result of reinfection or through the reactivation of a persistent infection it is usually impossible to determine, though occasionally the former event can be ruled out with almost complete certainty.

Now, though investigations into the common cold have proved peculiarly difficult, nevertheless even the failures here have, to my mind, emphasized the importance of host factors; for instance the failure to infect more than about half the volunteers in the Salisbury experiment under the most favourable conditions, including chilling, which has usually been considered a definite predisposing factor (fowls, of course, can be infected with anthrax only if they are first chilled). Why is the presence of a pathogen by itself insufficient to cause disease and, even when disease eventually results, why can the pathogen be present, often in considerable quantity and for hours, days, weeks, months or even years, without causing any symptoms and then suddenly show its teeth? What happens in the body of the host? Andrews (1949a) has demonstrated the presence of cold virus in the noses of his volunteers before symptoms developed, showing that the virus instilled into their nostrils had multiplied, that the infection had developed and that they were contagious, all in the absence of objective physical signs or symptoms of disease.

Herpes simplex provides, as Dubos (1954a) has pointed out, "a striking example of an infectious disease of man in which, contrary to the original tenets of the germ theory, the living agent of the disease (the germ) may be present all the time in the host—be intrinsic so to speak—whereas the determinant of the pathological process is some physiological disturbance or some other extrinsic factor of the physicochemical environment".

In recent years we have witnessed a striking and most unpleasant demonstration of how pathogens can lie doggo waiting to pounce. The orally administered antibiotics, which have often been so successful in banishing, for a time at least, the signs and symptoms of many diseases, have so profoundly changed the environment in the intestinal and respiratory tracts as on occasion to encourage some of their normal formerly peaceful inhabitants to spring into sinister activity, so that in the end the patient has been made more ill than by his original disease, or has even been killed. Whether the change of environment leading to this so-called "superinfection" is entirely "external", i.e. is due to the removal of the restraining influence of the natural antibiotics manufactured by the organisms which have been eliminated by treatment, or consists in an "internal" change taking place in the host's tissues, is unknown at present, but that an "internal" factor is at least involved seems to me very possible. In this connexion Murray's (1954) suggestions as to the way pathogens produce their effects is of great interest. "Disease", he writes, "even death, may not depend always on a necrotizing or lethal toxin secreted by the invading bacteria, and there may be no visible lesion. After all, the well-defined toxin of botulism causes definite symptoms and a high mortality without visible lesions, and though in pneumococcus infections visible lesions are not wanting, the process of their production is not clear. The active substance need not be antigenic or toxic, as is evident in the monocytosis of *Listeria* infection and in tuberculosis. But if capsular polysaccharides of bacteria can profoundly modify the "environment" within the tissues, as they do in the soil, some important new principle in pathology may emerge with a new assessment of antigenicity and toxicity."

In certain infections a restraining influence on the multiplication of the pathogens is apparently exercised by the monocytes which rapidly increase in numbers. This appears to be one of the "immunity" mechanisms operating in tuberculosis in which the monocytes seem to become endowed with this power (Dubos *et al.*, 1953) but it is important to note that the tubercle bacilli are never eradicated, their multiplication is merely retarded. Perhaps the most striking example of an induced protective monocytosis is that given by infection with *Listeria monocytogenes*, a fascinating account of which has lately been given by Murray (1953). He points out that the monocyte, which many people think is a transformed lymphocyte, is not pre-eminently a phagocytic cell, though it takes up tubercle bacilli to a moderate extent. It crams itself, however, with *Listeria*, living or dead, both *in vitro* and *in vivo* though refusing almost completely to ingest *Escherichia coli*. Now Stanley showed in 1950 that the selective monocytosis occurring in *Listeria* infection was entirely due to a chloroform-soluble lipid which could be extracted from the bacterial cell and he succeeded in extracting the same lipid from the liver of rabbits infected with *Listeria*, though he could not find it in normal liver. The important point about this lipid is that it is not antigenic or toxic. Its injection produces a monocytosis of much the same order as the infection does, but, as might be expected, of shorter duration. Animals with a monocytosis produce much more antibody than normal animals (though, as I have said, the lipid is not toxic or antigenic) but it is not justifiable to conclude that antibody is manufactured in the monocytes, it may be made elsewhere and merely stored in them, in which case this may explain the very rapid disappearance of passively introduced antibody from the circulating blood.

I would also call attention to some observations which suggest that "non-specific" host factors may have developed much earlier in the course of evolution than the "specific" ones. Burnet and Fenner (1949) in their monograph on the production of antibodies have considered the evidence collected by Irwin in his work at the University of Wisconsin on the blood groups of cattle, and by Traub (1936,

1938, 1939) (1953) have strain. All refer only to one strain of by injection preparation necrosis in the chick foreign cell long tolerance. I will not viz. the effect that abundance Caius in his England in same reason days before purging till same phenomenon to the veterinarian. *Clostridium* condition, found to be undernourished greater in very mild infected and malarial. Braxy sheep. As regards the disease phenomenon must continue work has, it has been aggressive in to *Pl. burgi* can be rendered with *Pl. knowle*. It is not established demonstration of the curative of penicillin of the death infections chemotherapy and again of sodium continued. The same workers in an antibiotic. Hart (1950) regard of interference native resistance. A very of host factors infectious resulting phenomenon or only a

1938, 1939) at the Rockefeller Institute, on infectious hepatitis; and Billingham, Brent and Medawar (1953) have done some remarkable work on the injection of embryo mice with cells from another strain. All these investigations suggest to me the late evolution of "specific" immunity, but I shall refer only to this last piece of work. Medawar and his co-workers showed that a skin graft taken from one strain of mice would take on a mouse of another strain only if the second mouse had been prepared by injecting it *in utero* with a suspension of spleen or other tissue from the first strain, but without this preparation of the foetus the graft on the young mouse provoked an immune reaction and underwent necrosis in a few days. They also succeeded in doing the same thing with chickens by inoculating the chick embryo with cells from a different strain of birds. In other words, in early development foreign cells are not recognized as such, and in fact their introduction into the embryo produces lifelong tolerance.

I will now return for a moment to an aspect of my subject to which I made brief reference earlier, viz. the effect of nutrition on resistance to infection. Speaking of resistance to tuberculosis I remarked that abundant nutrition does not always spell increased resistance. You will remember that Dr. Caius in his description of that curious epidemic disease which he calls "ephemera", and which struck England in 1551, remarks that "the laborious and the thin dieted escaped". (Perhaps it was for the same reason that patients were so dramatically prepared for arm to arm smallpox inoculation in the days before vaccination was introduced. Jenner tells us "there was bleeding till the blood was thin, purging till the body was wasted to a skeleton, and starving on vegetable diet to keep it so".) The same phenomenon has been observed in other diseases, but the evidence is, perhaps, more familiar to the veterinarians than to the doctors.

Clostridium infections in cattle and sheep seem to pick out the individuals in the most thriving condition, the poorer, thinner ones being unaffected, so that a short period of semi-starvation has been found to be a useful prophylactic measure. In foot and mouth disease both well-nourished and undernourished animals are affected, but the severity of the disease and the size of the lesions is much greater in the fat animals. Mr. M. Crawford tells me that though this disease is generally believed to be very mild in Indian cattle he has seen it take a very severe course in pure-bred Indian cattle which were fed and managed in the manner adopted in England for pedigree show cattle.

Braxy shows the same preference for thriving sheep rather than those in poor condition.

As regards man it is well known that malaria is usually a mild disease in breast-fed infants, though the disease is severer in children and adults not on a milk diet. Until lately no explanation of this phenomenon was known, though it had been supposed that the mother's milk—and in fact all milk—must contain some substance which protected against infection by the malarial parasite. Recent work has, however, pointed to quite a different explanation involving an important "host principle". It has been found that the malarial parasite requires PABA for its growth and fails to produce progressive infection if the diet of the infected animal is deficient in this vitamin. Thus rats are resistant to *Pl. burghesi* if fed on a milk diet, but susceptible if fed on a more complex food mixture, and rats can be rendered susceptible to the plasmodia by being fed on a milk diet supplemented with the vitamin or with folic acid. The same thing has been demonstrated for monkeys with regard to infection with *Pl. knowlesi* and *Pl. cynomolgi* (Dubos, 1954b).

It is not, of course, only in the resistance to invasion but also in overcoming the enemy when well established that host factors are important. A good illustration of this is given by Selbie's (1953) demonstration that sodium penicillin is as effective as either oily or aqueous procaine penicillin in the treatment of an experimental staphylococcal infection in mice. This result Selbie explains as due to the curative effects of penicillin depending not so much on the aggregate time that an effective level of penicillin is present in the blood as on other factors of which the most important is the co-operation of the defence mechanisms of the host. These mechanisms are so effective that staphylococcal infections in man and experimental animals are usually overcome by them in the end, even when chemotherapy is withheld, so that the part played by penicillin is to tip the scales in favour of the host and against the parasite, and this is done just as effectively by the hard blow delivered by a large dose of sodium penicillin, followed up by the host's defence mechanisms, as it is by a less intensive but more continued effect produced by procaine penicillin.

The same explanation is, perhaps, applicable to the success attained by myself and many other workers in the treatment of undulant fever by means of successive and comparatively short courses of an antibiotic such as aureomycin or terramycin.

Hart (1954) in a recent review of the host factors in tuberculosis has suggested that "we might regard some of the body's own defences as themselves acting like drugs... if it be accepted that interference with growth and survival of tubercle bacilli within macrophages is a feature of high native resistance and acquired immunity".

A very interesting and very obscure phenomenon which gives indirect evidence of the importance of host factors in controlling parasitism is the variation in the incidence and/or severity of many infectious diseases from year to year. With some diseases it seems probable that active immunity resulting from previous infection and eventually fading can account, at least in large measure, for this phenomenon, but in other diseases where the evidence suggests that there is no real acquired immunity, or only at best a very transient one, we must look for an explanation elsewhere. A good example

of this is the common cold. Andrewes and his co-workers (1953) believe that the resistance of the population to this virus may vary from year to year, as the percentage of volunteers at Salisbury who became infected fell from 55 to 60 in 1947, down to 30 in 1953. This might, of course, have been due to a fading of immune circulating antibodies, but Andrewes believes that resistance to cold infection is unrelated to the time which has elapsed since the last attack of the disease. In the case of poliomyelitis the picture is even more obscure, but it does not look to me at the moment as if the existence of specific antibodies resulting from experience of this pathogen is going to afford a complete explanation of the curious variations in its incidence from year to year.

I believe that we ought to consider very seriously the possible existence of what I will call, for want of a better name, "cosmic influences", by which I mean physical conditions in the widest sense which react on non-specific host factors increasing or decreasing their effectiveness. Such "cosmic influences" must, of course, be capable of affecting whole populations over a large area or over the entire world, but this is not, I think, an impossible conception. In illustration I will refer very briefly to a couple of remarkable epidemiological events for which no adequate explanation has, I believe, been found: the influenza pandemic of 1918 and the Ceylon malaria epidemic of 1934-35.

The influenza pandemic of 1918 presents an extraordinarily complicated picture and there has never been any general agreement as to why this major world catastrophe occurred. All I can do here is to mention a few facts which to my mind suggest that non-specific host factors may have played an important role in this event. In the Ministry of Health report (1920) on this pandemic the working hypothesis put forward was that the *materies morbi* (i.e. the influenza virus) though widespread for many years before this date had hitherto never been able to maintain its "dispersiveness", or toxicity at a high level until about 1889, by which time its infective power had become sufficient to produce outbreaks throughout the world at frequent intervals, and finally in 1918 the virus gained "complete victory" thanks to the "provision of countless incubators" in the form of garrisons, war-time factories, &c. Now this hypothesis is obviously inadequate. For instance in such countries as India the "countless incubators" had been there for centuries and were very little altered by the First World War. It is the sudden and pandemic nature of this outbreak which makes it so remarkable and which is so difficult to explain. I would not go so far as to say that the spread all over the world from person to person of a specially virulent strain of the virus from a single focus was an impossibility, but I find it hard to believe. For instance in the United States the first outbreak, so far as is known, occurred in Boston and was traced to cases in a destroyer flotilla which had lately come into port there, but other foci appeared in many parts of the States *within a few days* and were recognizable by the peculiarly toxic character of the disease and the unusually high mortality for such a disease as influenza.

As regards the epidemic in this country Andrewes (1949b) suggested that a series of virus mutants appeared in 1918, and Bradley (1952) supported this, but if this is true then either these mutants spread from a single focus, or some influence caused an exactly similar mutation in different parts of the world simultaneously. It seems to me that some "cosmic influence" may have so affected certain host factors that the pandemic took the particular form which was observed, owing either directly to a changed response of the host to the presence of the parasite, or indirectly to changes in the parasite produced by changes in its environment, i.e. the host's body. At any rate the old conception of the natural history of an epidemic being determined by the level of antibodies resulting from previous experience of the pathogen seems as inadequate to explain this particular experience as many people consider it to be as regards other outbreaks before and since.

Towards the end of 1934 a malaria epidemic started in Ceylon which was the most serious ever suffered by that country and, indeed, one of the most severe recorded anywhere. This epidemic, which I had the experience of studying on the spot, rose to a peak at the end of December 1934, and in April 1935, when this wave had subsided to almost the usual incidence for that time of the year, a severe secondary wave occurred. It was different from previous epidemics in Ceylon, of which records dating back to the middle of the seventeenth century are extant, in that the south-west quadrant of the island, which is a comparatively non-malarious area in normal years, was now the area chiefly affected. This unique occurrence, which was described in some detail by Briercliffe and myself (1936) in a paper to the Section of Epidemiology of this Society, presented some baffling features, and though the importance was generally accepted of such factors as the successive failure of the south-west monsoon, which occurs from April to September, and of the north-east monsoon, from October to March, which failure by drying up into pools the usually freely flowing streams in the south-west of the island afforded breeding places for *Anopheles culicifacies*; and also the lack of "salting" of the population in the south-west of the island, yet we both felt that such considerations were insufficient to account satisfactorily for all the phenomena observed. Though Gill's (1936) invocation of sun spots occurring in seven-year cycles to account for a "change in the parasite-host relationship" starting off this epidemic and causing a prevalence of malaria in Ceylon every seventh year, did not convince us at the time (and the prevalences did not seem to fit at all comfortably into his pattern) yet now I wonder if he may not after all have been on the right track, though I have no special knowledge of sun-spots and their possible effects.

It is easy, of course, to laugh at Sydenham's conception of epidemic "constitutions", and his idea

of "effluvia" enough to "constitute" that if he find the ke

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of "effluvia" due to "a certain and inexplicable alteration in the bowels of the earth", yet he was shrewd enough to notice and try to account for the ebb and flow of epidemic diseases and to realize that his "constitutions" could not be due to alterations of "heat, cold, dryness nor moisture". Who can say that if he were alive to-day with all the resources of modern knowledge at his disposal he might not find the key to this mystery.

Finally there are the extraordinary differences in the effects produced by the same pathogen in different species, a difference which must surely be due to non-specific host factors. Thus, as Murray (1953) has pointed out, the disease produced by *Listeria monocytogenes* "is predominantly a meningo-encephalitis in cattle, sheep, goats and swine . . . ; a metritis, with abortion, occurs in sheep, goats, swine and cattle and the micro-organism has been found in the genital tract of rabbits, guinea-pigs, horses, cattle, and humans; in birds there is a marked myocarditis which is also frequent in guinea-pigs; the disease is distemper-like in the fox; there is a conjunctivo-keratitis, which is quite peculiar in rabbits, guinea-pigs and horses; in many of these and in other animals it is a systemic infection marked by a necrotic hepatitis, but in the ferret it is a mild disease, almost a carrier state. In man many cases have been meningitis, some septicæmic; and a few cases in which *Listeria* has been isolated were clinically typical infectious mononucleosis".

Innumerable instances of the same kind can be adduced, such as the mildness of myxomatosis in the wild rabbits of South America, though it is so fatal to European rabbits; the acute nature of glanders in donkeys, though in horses it is usually a chronic infection; the very high resistance of Egyptian buffaloes to rinderpest, though Siamese and Ceylon buffaloes are highly susceptible; the complete absence of symptoms in wild game infected with nagana, though in cattle it is a fatal disease, &c.

CONCLUSION

In the short space of this address I have tried to show the importance of studying certain factors in the body's defence against the attacks of parasites, factors which I have termed for convenience the "non-specific physiological factors", and which I suggest have been too much neglected, so that a distorted picture has been presented of the interaction of host and parasite. I am conscious of the fact that in this review I have been forced by limitations of time to over-simplify the reactions of the body to bacterial invasion and to omit all mention of some recent important work on this subject, nor have I referred to certain interesting hypotheses which have lately been put forward to explain some of the body's reactions to infection and disease generally. Thus though the epidemiological, anatomical, physiological and other approaches are, I believe, important and should prove fruitful, yet the basic reactions are essentially biochemical and though our knowledge of them is still in an early stage it is already clear that they are of great complexity. I should have liked, had there been time, to say more about the experiments of Miles and others in elucidation of the events following bacterial invasion and the roles of "adaptive" and "constitutive" defences, and to talk of the very interesting work of Dubos, Ungar and others on the mechanism of inflammation—a return armed with modern weapons to a battle in which such pioneers as Pasteur and Calmette were once hotly engaged. Again whatever views may be held of Selye's conception of "stress" there can be no doubt that his work has been a powerful stimulus to the study of these fundamental problems and to the re-examination of our conceptions of what goes on inside the body. Another powerful stimulus to such studies has, of course, been provided by the availability of cortisone and ACTH as research weapons. It is quite clear that the endocrine system is closely concerned with the biological defences of the body, but a consideration of this aspect would need an address to itself.

I have indicated as I went along some of the directions in which research might prove profitable and some of the new methods now at our disposal, but there remains one, in a very early stage of development but with great potentialities, which deserves special mention—the new science of "gnatobiotics", or the study of germ-free life. This remarkable technique we owe to the inspiration, ingenuity and patience of Professor Reyniers of the University of Notre Dame, Indiana, who, in his own words "in an effort to satisfy my own curiosity and to provide experimental biology and medicine with a new tool", has created an apparatus and devised an elaborate method by which an animal's environment can be completely controlled from birth and healthy germ-free laboratory animals can be reared through successive generations (germ-free rats, for instance, have been reared through seven generations), thus not only proving the possibility of germ-free life, which had been doubted by Pasteur and many others, but also providing the experimentalist with a clean slate on which to write the biological effects of variations of the environment. The potentialities of this new science are obviously enormous, especially in the study of infectious disease, though, owing to the expense involved and the impossibility of transporting the apparatus, the experimenters must repair to Indiana or to one of the other (presumably very few) centres where a similar institute may be developed in the future.

I hope, then, that I have succeeded in this brief review in demonstrating the importance of studying the non-specific host factors concerned with parasitism and one of its expressions—"infectious disease". Murray (1954) has remarked that "it is likely that what is sought by the pathologist is still a formed lesion rather than a disturbance of function or deranged intracellular physiology". I would urge, then, that we adopt a new approach towards this subject.

Let us no longer think of infection and infectious disease as just a matter of a pathogen acting by means of its toxins and other antigens on a host and so producing a "disease", whereupon the host, under favourable conditions, produces protective antibodies with the help of which and his phagocytes, he overcomes the infection, if he is lucky, and slays the enemy. But rather let us say to ourselves here is a parasite which has obtained access to the host's body. The consequence may be either a comfortable symbiosis with no evidence of disease (though changes in the environment—which, of course, includes all the "host factors"—may at any time upset the balance between these two forms of life); or an immediate "defensive" reaction to the presence of the parasite may make life impossible for it; or, if this fails, a secondary "curative" reaction of the host may, after the development of the signs and symptoms of disease, eventually succeed in either killing the invader, or in establishing a comfortable symbiosis (which may involve the imprisonment of the invader in a tubercle, &c.) or finally there may be an uneasy "armistice" interrupted from time to time by disturbing "incidents". And if as doctors and veterinarians we want to find out about the complicated host mechanisms involved, so as to help our patients to ward off the invader or to prevent the unpleasant consequences of imbalance between host and parasite, or to replace "dis-ease" by "ease", we must devote our attention not only to such factors as so-called "specific immunity", phagocytosis, antibody formation, &c., but to all the natural mechanisms of the body by which those species with whose welfare we are concerned manage to survive in intimate contact with innumerable microscopic species, which are not always friendly towards them. By adopting such an outlook and investigating these general factors we may finally discover secrets which will enable us to protect men and animals, not only against particular parasites, but against all, and in doing so perhaps shed light as well on conditions which are not of parasitic origin.

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Section of Pathology

President—L. P. GARROD, M.D., F.R.C.P.

[October 19, 1954]

Chemicals versus Bacteria

PRESIDENT'S ADDRESS

By L. P. GARROD, M.D., F.R.C.P.

THE possibilities of combating bacterial infection by chemical means have interested me for nearly thirty years. Throughout that time I have been impressed by remarkable divergences of belief and practice in connexion with this subject. This has been true of all three branches of it, which may be referred to as disinfection, antiseptis and chemotherapy. Such disagreements were only possible because of conflicting data, and if data are in direct conflict, some of them must have been obtained by improper methods. I would like therefore particularly to consider the value of different methods in attaining knowledge in these matters. The clinician relies increasingly on the bacteriologist for guidance in almost all matters pertaining to infection. It is on tests made in the laboratory that he must rely in deciding whether or no any proceeding is likely to be successful. We must therefore be able to make such tests, and the choice of their method is of some importance.

HISTORICAL

The undoubted father of this whole subject, to whom it seems to me far too little honour is given, was Semmelweis, who introduced disinfection of the surgeon's hands with chlorinated lime as a preventive of puerperal fever in 1847. In spite of the striking success of this measure, of which he furnished the fullest statistical proof, he was derided and opposed, even by such an authority as Virchow, and died, a disappointed man, before his work had gained general recognition.

Twenty years after Semmelweis's discovery, the antiseptic treatment of wounds was introduced by Lister. This, too, met with opposition, but Lister was far better qualified by character, personality and professional distinction to sustain it; his doctrine prevailed, and he became one of the most honoured figures in the whole history of surgery. It has been fashionable since then to dismiss the antiseptic method as only a stage on the way to the aseptic, which we owe to von Bergmann. This has always seemed to me a false antithesis; these are not alternative or rival methods, but each is complementary to the other. Most of the paraphernalia of surgery is best sterilized by heat, but if bacteria are to be killed on the skin or in a wound, physical methods must give way to chemical. It is one of my purposes to show that not only skin disinfection, but some useful degree of disinfection of a recent wound, is feasible—in fact that Lister's principles are still applicable in the light of modern knowledge.

The chemotherapy of bacterial infections—I am not considering protozoal—dates from the introduction of salvarsan for the treatment of syphilis in 1909. It is worth considering whether this drug had any other proper uses; I shall suggest that it had, and offer some evidence in support of the suggestion. For a further twenty-six years all other attempts at the chemotherapy of systemic infections—and many were made—were futile. Then in 1935 came the sulphonamides and in 1940 the first antibiotic, and chemotherapy from being an unattainable ideal has become a commonplace of everyday practice.

SKIN DISINFECTION

Despite a history going back over a hundred years, this subject has by no means reached finality. Not only does individual practice vary, but some brisk little public controversies have been going on recently between exponents of rival methods. One of these was between Neufeld (Neufeld and Schütz, 1941; Neufeld, 1943) who champions spirit, and Gottsacker (1942) who is an advocate of Zephyrol. In connexion with Zephyrol and other quaternary ammonium compounds it seems that history nearly seventy years old is repeating itself. The findings of Koch in relation to mercury perchloride were shown by Geppert (1889) to be spurious because he had taken no steps to neutralize

the disinfectant carried over into the culture, and even traces of mercury salts will prevent the growth of bacteria on which they have already acted without killing them. The quaternary ammonium compounds, or "quats", of which Cetrimide is the best known in this country, behave similarly, and unless they are neutralized, as they can be by lecithin, milk powder, &c. (Weber and Black, 1948), fantastic and entirely spurious results can be obtained in short-term disinfection tests. My colleague Story (1952), who observed this precaution in skin disinfection tests with Cetrimide and other quats, found them to be inefficient. There is also the question whether quats really disinfect the skin or merely cover it with an antiseptic film beneath which many bacteria survive. According to Naumann (1952) this film can be broken by applying serum, or by the novel proceeding of introducing the treated hand into the peritoneal cavity of a dog: it then again gives off numerous bacteria.

The importance of method, to which I have already referred, is evident here. I will not venture to suggest which of many methods, some very elaborate (Price, 1938) or peculiar (Nungester and Kempf, 1942), which have been used for testing skin disinfectants, is the most appropriate, although it would seem that destruction of a pathogenic organism with which skin has been contaminated is a more reasonable aim than suppression of the normal flora: I would only submit that this subject merits further work.

The question of compatibility must not be forgotten: Some of my surgical colleagues were in the habit of preparing skin with Cetrimide solution followed by tincture of iodine, and I was asked my opinion of this. Neither I nor high pharmaceutical authorities whom I consulted could pronounce on the possibility of interaction between these two solutions, so I tested it by the simple method of adding one to the other. The result was the instantaneous formation of a thick deposit like cocoa.

WOUND ANTISEPSIS

It has been said (Wright, 1916) that Lister's achievement was in "showing that septic infections of surgical wounds can be prevented by the use of antiseptics". The use of the word "surgical" excludes traumatic wounds, and the question I wish to examine is the usefulness of antiseptics in preventing infection in these also. How far did Lister's work support the proposition that this is feasible? The following is part of his own account of one of the first cases so treated, a boy aged 7 who had been knocked down by an omnibus, crowded with passengers, one or both wheels of which had passed over his leg:

"The tibia, which was broken about its middle, lay exposed in a wound occupying almost the entire length and breadth of the inner aspect of the leg . . . the skin having been stripped back so as to lay bare the gastrocnemius as well as the bone . . . Chloroform having been administered, the acid of full strength was applied with great freedom, the contused mass being repeatedly squeezed to induce the liquid to insinuate itself into all the interstices, including that between the riding fragments of the tibia. The flap of skin was then brought towards its natural position, and lint soaked in the acid was placed upon the wide raw surface which still remained exposed. . ."

The first reflection prompted by this case history is that the patient was fortunate not to have died of carbolic acid poisoning or of the secondary effects of extensive tissue necrosis. That he did not is a tribute to the capacity of the body to withstand chemical insults. Nobody would use such treatment to-day, and Lister himself later reduced the strength of his phenol solutions to 5% or less, but if a single application of so appallingly toxic a substance can in fact be tolerated, has there not been some exaggeration of the harm which can be done by less noxious antiseptics which have been developed since?

In what I have further to say I am concerned almost solely with the prevention of sepsis in accidental wounds, and not with its treatment, which is a very different thing. The question is quite simple: pathogenic bacteria may be implanted in a wound at the time of its infliction: is it possible by chemical means to destroy them or so to diminish their numbers as to reduce the risk of infection developing? Lister evidently believed this to be possible, although admittedly his writings deal chiefly with barring the access of bacteria to surgical wounds rather than with disinfection of fresh contaminated traumatic ones.

There is very little to record in connexion with this subject for nearly fifty years after Lister's discovery except the introduction of many alternatives to carbolic acid, each of which had its adherents. I have quoted before (Garrod and Keynes, 1937) a passage from a well-known textbook of surgery which typifies the attitude of these times:

"Hæmostasis is effected, and the wound cavity temporarily packed with gauze soaked in some suitable antiseptic (for example, iodine, carbolic lotion 1 in 20, a strong solution of brilliant green, or any other that the surgeon favours)."

There are two astonishing ideas in this: (1) that three antiseptics having totally different properties can be equally suitable for the purpose; (2) that personal preference, exercised somewhat as in choosing a wallpaper, can lead to a suitable choice. It is safe to say that throughout this time very little good was done by such applications.

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With the outbreak of the First World War it became acutely necessary to formulate some definite belief about the usefulness of antiseptic wound treatment. Cheyne (1915-16), then President of the Royal College of Surgeons, preached a return to Listerism, with the use of strong preparations of phenol and cresols: Wright (1916), in a devastating reply, tore his arguments to shreds. It does not seem that Wright entirely denied the possibility of disinfecting a wound chemically, indeed he specifically admits that Lister may have succeeded in doing so in the case, the account of which I have already quoted. On the other hand, he denies the possibility of any useful effect in penetrating wounds the depths of which are inaccessible, and in wounds of which the treatment is delayed. Most casualties in France belonged to both of these categories, and were in fact very unpromising material in which to study this question anew.

ACRIFLAVINE

Another polemic in which almost equally strong language was used was between Browning (Browning, Gulbransen, Kennaway and Thornton, 1917; Browning, Gulbransen and Thornton, 1917), and Fleming (1917) on the merits of acriflavine. This antiseptic was also used during the latter part of the war, and according to Drummond and McNee (1917) its use under favourable conditions prevented sepsis. Leaving aside for the moment the question of its possible clinical usefulness, this substance affords an interesting opportunity of inquiring into the merits of different methods of laboratory assay. A purely *in vitro* method of assessing both antibacterial activity and toxicity to tissues is to determine the concentrations (1) inhibiting bacterial growth, (2) inhibiting leucocytic activity, whether motility or phagocytosis. Very much depends on the conditions of such experiments. Browning, using conditions highly favourable to the antiseptic—a very small bacterial inoculum and a short period of action on leucocytes—found the concentration inhibiting bacterial growth to be 400 times less than that inhibiting phagocytosis, and thus credited acriflavine with a "therapeutic coefficient" of 400. According to Fleming, if contact with leucocytes is prolonged to twenty-four hours, acriflavine is lethal even at 1 in 2,000,000. Since varying the bacterial inoculum could also make an 80-fold difference, he concludes that "the so-called 'therapeutic coefficient' of flavine can be changed with slight variation of the experimental method by at least 300,000 times".

This is a fantastic difference, and it seems that if tests with leucocytes are to be accorded significance, there should be general agreement on how they are to be done. The stated lethal concentration of 1 in 2,000,000 is not borne out by Fleming's own later observations (1924, 1940) made by a different method, that of the slide cell. In the first of these the absence of an anti-leucocytic effect in concentrations of from 1 in 5,000 to 1 in 320,000 is explained by assuming that phagocytosis had occurred before the leucocytes were killed: in the second, when bacteria were added at a later stage, there was an anti-leucocytic effect at 1 in 270,000 but little or none at 1 in 810,000. It seems difficult to decide from such data what concentration of acriflavine leucocytes can withstand if exposed to it for long periods: on the other hand, it is quite clear that during shorter periods they retain motility and the capacity for phagocytosis in the presence of concentrations which are antiseptically effective. That these are not damaging to other tissues also seems clear from the histological studies of Bennett, Blacklock and Browning (1922) and Blacklock (1928-29). In any case it is now known that neutral proflavine and the newer acridines have a lower tissue toxicity than acriflavine, and they have replaced it in clinical use.

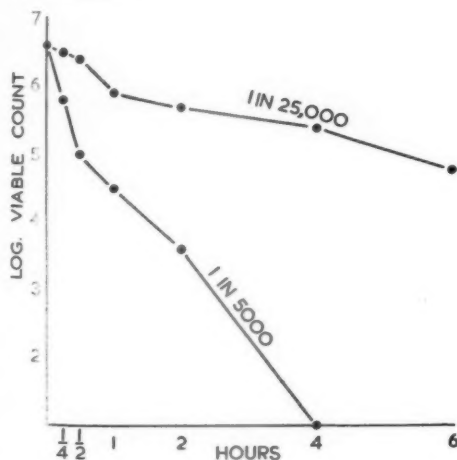


FIG. 1.—Rate of killing of *Staph. pyogenes* in broth at 37° by two concentrations of proflavine.

Most of the earlier information about the action of acridines on bacteria refers only to inhibition of growth, and I have recently thought it worth while to make some fresh experiments on bactericidal action, and how its rate is affected by some of the factors which entered into the argument of nearly forty years ago. I used proflavine hemisulphate, and *Staph. pyogenes* as the test organism; this is less sensitive than *Streptococcus pyogenes*, but chain formation by the latter makes viable counts inaccurate. The effect of concentration is illustrated in Fig. 1: 1 in 5,000—a concentration maintainable in a wound—takes four hours to exterminate a large inoculum, but on the other hand it produces a 98% mortality within thirty minutes. Even 1 in 25,000 is slowly bactericidal. In Fig. 2 the death-

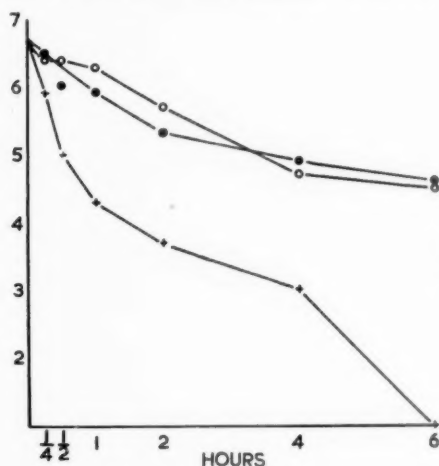


FIG. 2.—Rate of killing of *Staph. pyogenes* at 37° by 1 in 5,000 proflavine in + broth, O serum, ● blood. (The results in broth although apparently indicating slower killing than in Fig. 1, are almost identical except that there were 0.016% of survivors at four hours.)

rate produced by 1 in 5,000 in broth is compared with that in serum and blood. In each of the latter it is slower—to an almost equal degree: thus the alleged greater activity of acriflavine in serum is at least not confirmed for proflavine. The effect of inoculum size is shown in Fig. 3. The 4 inocula

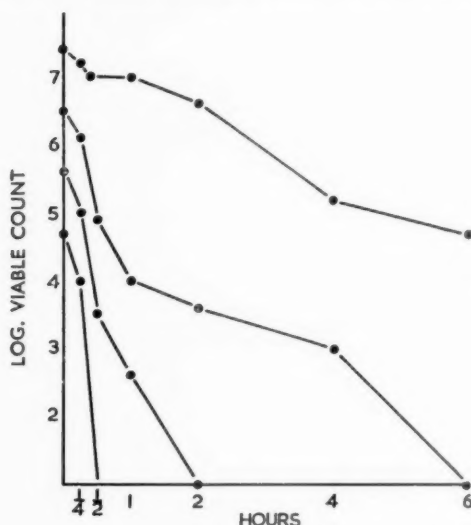


FIG. 3.—Rate of killing of *Staph. pyogenes* in broth at 37° by 1 in 5,000 proflavine: effect of inoculum size.

differed by 10-fold, and although the smallest is naturally exterminated most quickly, killing is progressive in that 1,000 times greater: there is thus no suggestion that a large inoculum has a saturating and inactivating effect.

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It may be objected to these experiments that no control substance was used for comparison. On the other hand, it is equally an axiom that in such tests like should be compared with like, and I know of no similar substance with which comparison could be made. In their activity in high dilution in such media as serum and blood the acridines are unique among antiseptics.

ANIMAL EXPERIMENTS WITH ACRIDINES

There is another way of testing a wound antiseptic; to imitate in an animal the task it is expected to perform in man. A mouse can be inoculated locally with a lethal dose of streptococci or other bacteria, and the area can be treated, either forthwith or after an interval, the efficacy of treatment being judged by survival or death. Many series of experiments of this kind were done, chiefly by German workers in the early twenties, all giving similar and highly significant results, and others have confirmed them since. Several methods of inoculation and antiseptic application were used. Morgenroth and Abraham (1920) and later Hata (1932) injected the inoculum subcutaneously and infiltrated the surrounding area with antiseptic. Schiemann and Wreschner (1922) and Weise (1922) inoculated a wound made by skin incision and applied the antiseptic to this: Collier and Bernhagen (1928) and later Gordon *et al.* (1947) made an open wound by removing an area of skin with scissors: Feiler (1921) and Browning and Gulbrandsen (1925) undercut double incisions which were inoculated with *C. diphtheriae*: McIntosh and Selbie (1943) inoculated mice intramuscularly with *Cl. welchii* and injected the antiseptic at the same site later.

The results of all these experiments point to the same conclusion: that whereas the older antiseptics are powerless to disinfect tissue inoculated with virulent bacteria (the single exception is the occasional success of phenol against *C. diphtheriae*, explicable by the non-invasiveness of this organism) acriflavine and related acridine compounds will save a substantial proportion of animals if applied within one or two hours—i.e. before bacterial invasion of the tissues has placed them beyond the reach of external applications.

It seems to me that evidence of this kind overrides all forms of *in vitro* test. In particular the survival of the whole animal must take precedence over findings in connexion with one of its cells, the leucocyte. Even if an effective application does kill some leucocytes it probably matters little; plenty more will take their place. I venture to suggest that too much preoccupation with the behaviour of leucocytes, especially under highly artificial conditions, has been misleading. If such experiments lead to the conclusion that all antiseptics do more harm than good, then so far as the acridines are concerned the conclusion is false and the method must be faulty. This doctrine of the general uselessness of antiseptics may be said to have hindered possible progress in this field for over twenty years.

LATER HISTORY OF THE ACRIDINES

The form in which acriflavine was commonly used for long after the First World War was the B.P.C. Emulsion, a pharmacist's concoction so devised as to be almost inert. What may be called the rehabilitation of the acridines was due to several factors. Foremost was the work of Albert (for review see Albert, 1951) who synthesized many new compounds, related their structure to their activity, and established the superiority of proflavine and other compounds over the original acriflavine itself. Russell and Falconer (1940-41) did an important service by pointing out that if an antiseptic solution is to do no harm it must be isotonic and buffered to a reasonable pH: proflavine so prepared in 0.1% solution was found to be no more harmful than saline to the exposed rabbit brain. These findings and the revival of belief in the usefulness of local applications to wounds which was brought about by the use of sulphonamide powders led to the re-employment of acridines, chiefly proflavine, in more rational ways. But for the advent of penicillin the standard application to wounds to-day would probably be the 1% proflavine-sulphathiazole powder which was used so successfully at the Middlesex Hospital (McIntosh *et al.*, 1945) and elsewhere (Williams and Miles, 1949) during and after the Second World War. These observations had to do with the prevention of sepsis, but other authors (Mitchell and Buttle, 1942; Poate, 1944a, b) firmly assert that established suppuration can be successfully treated with proflavine or 5-aminoacridine powders.

HIBITANE

As a recent development in studies of antiseptics it is appropriate to mention bis-*p*-chlorophenyldiguanidohexane ("Hibitane"), preliminary work on which has been described by Davies, Francis and Martin (1954). I am indebted to Dr. A. R. Martin for further particulars of infection-prevention tests in mice done with this substance. In these later and hitherto unpublished tests the needle through which a lethal inoculum of streptococcus culture was injected subcutaneously in mice was left *in situ*, and the antiseptic was injected through it one hour later, a neat variation on previous methods of doing such tests which others may find it useful to copy. Under the conditions of this

test, various other antiseptics failed to save a single mouse, but Hibitane in equivalent concentrations was more effective than proflavine (Table I).

TABLE I.
COMPARISON OF HIBITANE AND PROFLAVINE
IN PROPHYLAXIS OF STREPTOCOCCAL INFECTION IN MICE

Treatment	No. of mice	No. of deaths	% survival
Hibitane diacetate 0.1%	20	2	90
" " 0.05%	40	8	80
" " 0.02%	20	7	65
Proflavine 0.1%	20	14	30
" 0.05%	20	19	5
" 0.02%	20	20	0
None	20	20	0

Organism — *Str. pyogenes* in horse blood.

Inoculation — Subcutaneous injection.

Treatment — drug injected twenty minutes later *via* same needle left in situ (drug also dissolved in horse blood).

(A. R. Martin (1954) Personal communication.)

So far as the relative efficacy of Hibitane and acridines is concerned, these findings need perhaps to be verified by varying the conditions of the test. They nevertheless suggest two questions: (1) Has the possible existence of compounds with superior antiseptic action been adequately explored? (2) What use can be made of such a substance or perhaps a better one should it be discovered?

It will not take anyone who is acquainted with present trends in the general warfare against bacteria long to answer the second question. Staphylococci are getting out of hand: from being resistant to penicillin and the tetracyclines, they are now recorded (Martin *et al.*, 1954) as resistant also to erythromycin, which at present is the last antibiotic line of defence against them. A preventive of staphylococcal infection, if only in operation wounds in a surgical unit infested with an antibiotic-resistant staphylococcus, might be a useful safeguard. Hibitane is being tested in my own hospital in this capacity at the present time, but further experience will be necessary before its usefulness or otherwise can be established.

CHEMOTHERAPY

Salvarsan was the first drug to act systemically on any other organism than protozoa, and general progress in the chemotherapy of bacterial infections had to await the introduction of the sulphonamides over twenty-five years later. This is not to say that no attempts were made: I was myself directed when I was a house physician to treat a case of bacterial endocarditis by intravenous injections of mercury perchloride solution, and did so. There was even some slight foundation for this (Fleming, 1931) and, absurd as such proceedings were, we should even credit the advocates of intravenous Eusol (J. Lorrain Smith *et al.*, 1915; Fraser and Bates, 1916*a, b*) with having declared that their object was to combat toxæmia: they nowhere claim that this treatment killed bacteria in the blood.

The claims made for mercurochrome, which had an immense vogue in the twenties and was seriously believed by many people to be an efficient intravenous antiseptic, were extensive, detailed and quite fantastic. Faulty laboratory work and credulous clinical observation have rarely perpetrated a therapeutic fraud on such a scale. Mercurochrome in 0.1% solution was said to kill bacteria in one minute (Young *et al.*, 1919)—a rapidity of effect of which no mercury compound is capable under any conditions—and intravenous injection in animals was said to confer bactericidal properties on the blood, urine and bile (Young *et al.*, 1925). How many technical errors—besides disregard of pH and failure to include an inactivator in culture media—may have contributed to these wildly erroneous results it is difficult to say. Like some other workers at the time I found mercurochrome quite incapable of doing what was claimed for it, and took some pleasure in raising my voice in protest at what was going on (Garrod, 1931*a, b*).

If any bacterial infections were susceptible to chemotherapy during this period the effective drug was salvarsan or one of its successors. These were used, sometimes with apparently good effect, in streptococcal septicæmia, and Colebrook (1928) showed that the serum of patients was bactericidal for hæmolytic streptococci for some hours after a dose of neoarsphenamine. He also tested the action of this drug on four other species of bacteria, but did not include the anthrax bacillus. The regular efficacy of the organic arsenicals in anthrax is beyond question; Pijper (1926) describes a series of 40 cases treated exclusively with salvarsan without a single death. Never having seen any comparison of the susceptibility of *Str. pyogenes* and *B. anthracis* to neoarsphenamine I recently made one, using four strains of each organism. All strains of the latter were inhibited by the concentration of

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0.00005 M (1 in 43,000), whereas the concentration required to inhibit *Str. pyogenes* was four times greater (Table II).

TABLE II.

CONCENTRATIONS OF NEOARSPHENAMINE
INHIBITING 4 STRAINS EACH OF *B. anthracis* AND *Str. pyogenes* IN 10% SERUM BROTH AT 37°—24 HOUR

			Concentration					
			0.0002 M	0.0001 M	0.00005 M	0.00002 M	0.00001 M	0.000005 M
<i>B. anthracis</i>	—	—	—	+	+	+
"	—	—	—	+	+	+
"	—	—	—	+	+	+
"	—	—	—	+	+	+
<i>Str. pyogenes</i> (A)	—	+	+	+	+	+
"	—	+	+	+	+	+
"	—	+	+	+	+	+
"	—	+	+	+	+	+

This is perhaps not the only reason for the difference in therapeutic effect. Anthrax is a cellulitis going on to septicaemia: there is no necrosis or suppuration, and a drug in the blood therefore penetrates the whole affected area completely. Its task is therefore easy compared with that in, for instance, puerperal septicaemia, where there used to be septic thrombi in uterine veins and often metastatic abscesses before some desperate therapeutic measures were undertaken.

THE CONTRIBUTION OF THE LABORATORY TO-DAY

The position to-day is very different, and the hospital bacteriologist spends much of his time in enabling the clinician to choose between a dozen new drugs, each a chemotherapeutic agent with powers undreamed of twenty years ago. In this new branch of bacteriology method is again all-important if reliable results are to be obtained. In the literature of this subject there are many examples of sulphonamide sensitivity tests conducted without due regard to sulphonamide inhibitors in the medium or to the effect of inoculum size. In antibiotic sensitivity tests the composition and pH of the medium are of little importance except in tests with streptomycin and chlortetracycline, but inoculum size is important, as are the concentrations of antibiotics used, the rate of growth of the organism, and the period of incubation. In view of the finding of Jackson and Finland (1951) that results, particularly with chlortetracycline, can vary so widely according to the method used, it is astonishing to read a recent American paper (Welch *et al.*, 1954) claiming to have shown that chlortetracycline has about twice the activity of tetracycline and four times that of oxytetracycline against staphylococci without giving any particulars of how the tests were done.

Many laboratories are using time-consuming methods, extravagant of material, without any commensurate gain in accuracy (Eisenberg and Wagner, 1952; Schwarz and Brown, 1954; Bérens and Guillaume, 1954). For ordinary purposes I am unashamedly in favour of the disc or cup method in primary culture: the main conditions necessary for success in this are an inoculum of the right size and uniform spreading, and this is impossible with the wire loop so often used.

I would conclude with a plea that the bacteriologist should interest himself not only in chemotherapy, but in the uses of more ordinary chemicals in dealing with bacteria. The surgeon depends largely on us for guidance in how to do the simplest things. I have already referred to the confusion to which still exists about how to disinfect the skin. There are probably still hospitals in which patients deemed to have recovered from an infectious disease are given a "carbolic bath" containing an amount of phenol six times too weak to have any bactericidal effect. I have been consulted about how to sterilize various ligature materials, catheters, instruments—particularly 'scopes—baths, bedpans, anaesthetic apparatus and marine sponges, and how to disinfect all manner of things from books and blankets, telephones, thermometers and tooth-brushes to a crocodile-skin handbag belonging to a patient with typhoid. Quite recently I was called upon to investigate the claim that a proprietary solution would sterilize syringes: it was said even to be lethal to spores in three minutes. Of course these claims were baseless: the manufacturers had evidently been misled by experiments performed in ignorance of the pitfalls of such work. Such matters as these, and the use made of antiseptics in a Casualty Department, may be rather dull, but they can sometimes affect the patient's well-being quite as much as the choice of an antibiotic for him, and the medical bacteriologist cannot afford to ignore them.

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BOOK REVIEWS

Tumours of Lymphoid Tissue. By George Lumb, M.D. (Pp. viii+204; illustrated. 37s. 6d.)
Edinburgh and London: E. & S. Livingstone Ltd. 1954.

This monograph embodies the author's extensive experience in the pathology, prognosis and treatment of tumours of lymph nodes. It is based mainly on a lengthy personal study of over 400 such cases at the Westminster Hospital in London, but it is also documented adequately with references to British, American and Continental literature.

The nomenclature of tumours of lymph nodes has long been based chiefly on their differing histological structures, and in recent years the introduction of new names has rendered such classifications increasingly elaborate and unfamiliar to any but the expert. The present author's reversion to a simpler and more direct terminology will therefore be welcomed widely by both clinicians and pathologists alike. Essentially, Dr. Lumb has divided these neoplasms into four major categories according to the type of cell that has undergone proliferation: (i) lymphocytes; (ii) reticulum cells; (iii) mixed cells; and (iv) anaplastic variants of any of the former. Within these four main groups, he has made several subcategories, but throughout the classification remains simple and logical. Moreover, for most readers it possesses the great advantage that it employs familiar names, used for the most part with connotations that are widely accepted.

Much of the book is taken up with systematic descriptions of the various types of tumour, their presenting signs, relative frequencies, morphological features and prognoses. Of noteworthy value and interest to pathologists is the chapter in which the problems of diagnosis are reviewed and the techniques of biopsy described. Here the differential diagnosis of the various tumour types is considered in detail together with the avoidance of their possible confusion with certain forms of chronic inflammatory lesions in lymph nodes.

The book should prove useful to both clinicians and pathologists. It contains a large amount of information on an important group of neoplasms in a volume of moderate size. Almost all the 184 illustrations—most of them photomicrographs—are excellent and should prove helpful to surgical histologists. The format of the book is very good and misprints are rare.

Coronary Heart Disease in Young Adults. By Menard M. Gertler, M.D., and Paul D. White, M.D. (Pp. xx+218; 11 illustrations. 40s.) Harvard University Press. London: Geoffrey Cumberlege. 1954.

This book of 218 pages outlines an investigation which had as its purpose the finding of any factor which predetermines cardiac infarction in any erstwhile healthy subject. One hundred patients with unequivocal and electrocardiographic evidence of cardiac infarction, under the age of 40, were matched with a control group which tallied in age, height, weight, body build, race and occupation.

In the course of this exhaustive study which included a consideration of sex, morphological characteristics, heredity, serum cholesterol, serum uric acid, cholesterol and lipid phosphorus ratio, and salivary redox potential, the authors tried to uncover some signal which might tell in what kind of individual cardiac infarction is likely to take place. If such prediction is possible it follows naturally that some form of preventive therapy might be tried in order to delay the onset of the heart attack.

They conclude that coronary heart disease is predominantly a male affection before the age of 40 years. There appears to be a relation between season of the year and infarction for 60% of the severe episodes occurred during the five-month period between November and March. Coronary heart disease is more likely to take place in individuals if mother, father, or siblings have suffered from the disease. In the test group there was a preponderance of Jews and a scarcity of Negroes.

There has long been speculation concerning the relation between body build, body weight, and longevity. The investigation demonstrated clearly that the endomorphic mesomorph (the fat muscular person) is most prone to cardiac infarction, and the ectomorph (the lean person) is least prone.

Cholesterol by itself is doubtless an important aetiological agent in coronary heart disease, but it is only one link in the chain which is made up of others including thyroid and adrenal influence, arterial intimal thickening, colloidal stability which is partially controlled by lipid phosphorus, and the rate of both anabolism and catabolism of cholesterol within the arterial walls. Although an association exists between the level of serum lipids and clinical atherosclerosis, a causal relation between ingested lipids, including cholesterol, and atherosclerosis, has not yet been proved.

Although the patients with cardiac infarction consumed alcohol and used tobacco in larger quantities than the control group, the findings did not warrant judgment on the causal relation between these agents and coronary heart disease.

Although no hard and fast conclusions are drawn on the cause of atherosclerosis of the coronary arteries, this work represents an earnest attempt to uncover possible sources that have not been explored in the past with such thoroughness as has been shown in this book.

Biochemical Investigations in Diagnosis and Treatment. By J. D. N. Nabarro, M.D., M.R.C.P. (Pp. x+299; 5 illustrations including 1 plate. 25s.) London: H. K. Lewis & Co. Ltd.

This book is designed to assist the hospital resident and registrar to apply the results of the relevant biochemical investigations to the diagnosis and treatment of disease. Consequently, details of the methods by which the results are obtained are largely omitted, thus allowing smoother discussion. When the manner of taking the sample, or the time, or some other special precaution is of importance, this is given in adequate detail. There is a great increase in the numbers of tests to which a patient may now be submitted; the author wisely indicates which are the most useful, for which the patient and routine laboratory will be grateful, and he preserves a sense of proportion by indicating what the physician can normally expect from a routine laboratory as distinct from a research department. The book may be regarded as being composed of two complementary sections, the first, dealing with the metabolic changes of various single body constituents in disease, and the second dealing with biochemical changes consequent upon disease of specific bodily systems. The early chapters deal with sodium and water metabolism, acid-base equilibrium, potassium, magnesium, iron and copper, calcium and phosphorus, protein and nitrogen metabolism, carbohydrate and fat metabolism. The later chapters deal with the changes occurring in various disease conditions in the gastro-intestinal tract, pancreas, liver and biliary tract, etc. The section on changes occurring in various endocrine conditions is particularly useful—among other things the complex inter-relationships involved and the potential dangers of ACTH and cortisone therapy are adequately indicated. This is followed by two short chapters on the effects of vitamins and certain types of poisoning. Most of the sections are followed by a small series of references for such further selected reading as will give the reader rapid access to the main literature of the field. Altogether this is a very practical book, a useful guide for the clinician to get the most out of his laboratory investigations. At the end of the book there is a very useful series of tables of the normal biochemical constants—subdivided into those to be expected from the routine and those from the research laboratory, requiring very special techniques. The sources of the figures are also indicated.

Antisera, Toxoids, Vaccines and Tuberculin in Prophylaxis and Treatment. By H. J. Parish, M.D., F.R.C.P.E., D.P.H. 3rd edition. (Pp. x+227; illustrated. 21s.) Edinburgh and London: E. & S. Livingstone Ltd. 1954.

Though the title of the two previous editions of this book was not strictly inaccurate, it was a little misleading if the subtitle was not included; so it is good to see the words "Bacterial and Virus Diseases" deleted from it.

The book is evidently intended to be a treatise on the practical aspects of immunology, suitable for medical students and general practitioners; for this purpose it is admirably adapted. After a short introduction on the principles of immunology, it gives a clear, simple, up-to-date and moderate account of the nature, use, advantages and disadvantages of the various prophylactic and therapeutic immunological agents used in man, with a thorough description of the technical methods employed. These include sterilization of syringes, care of needles, the administration of prophylactics and sera, and the prevention of serum reactions. There are also elementary descriptions of the methods of manufacture of some of the products recommended.

The presentation is generally clear, though sometimes rather repetitive; is there any need, for instance, to repeat the information on passive immunity on p. 6 and on the lower half of p. 7? The figures are usually good and informative, though those on pp. 179–181 are perhaps no longer necessary, and could be usefully replaced by more photographs of notable immunologists.

Elizabeth Tudor: The Lonely Queen. By Sir Arthur S. MacNalty, K.C.B., M.D., F.R.C.P., F.R.C.S., Hon. F.R.S. (Pp. 272. 18s.) London: Christopher Johnson Ltd. 1954.

The learned author of this book has already shown his special knowledge of Tudor times by his work on Henry VIII, a Difficult Patient; he deals here with the life of Queen Elizabeth, considered specially from the medical aspect. Certainly to a doctor the most interesting chapter in the book is that entitled "The Queen's medical case-sheet". Here, in a brief 22 pages, we have a connected account of all the illnesses which afflicted the queen during her long life. Smallpox, chicken-pox, nephritis, migraine, and other ailments which attacked her, are all recounted and, *horribile dictu*, the author tries to persuade us that she was subject to attacks of hysteria. We found this difficult to credit. It is sad to learn that Elizabeth became bald as the result of an attack of smallpox at the early age of 31.

The author obviously greatly admires the Queen who ruled so cleverly for so many years. On several occasions when Elizabeth apparently acted unfairly or harshly the censure which would naturally be pronounced is mitigated by the statement that the Queen at that time was in ill-health. We wonder what changes in historical judgments might occur if this principle were generally applied. We are not given any indication that irony is intended when it is stated that Elizabeth was "for once less magnanimous than was her wont" when she had caused to be executed seven hundred of the rank and file of those who rebelled against her in 1569.

The author ends an interesting study by giving a list of all the husbands who were at one time or

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another proposed for Queen Elizabeth. There were more than two dozen of them. There is also a list of her physicians but this is rather incomplete and we are referred elsewhere for further details.

We think this book will be widely read, as it well deserves to be. It reads easily and, with one slight exception, there are no misprints.

Heart: A Physiologic and Clinical Study of Cardiovascular Diseases. By Aldo A. Luisada, M.D. 2nd edition. (Pp. xiv+680; 312 illustrations. 114s.) London: Baillière, Tindall and Cox Ltd. 1954.

This book, now in its second edition, is intended for undergraduate and postgraduate students. It is magnificently produced and illustrated. The simple aetiological classification of diseases of the heart has been correlated with anatomicoclinical syndromes which the author favours and which the reader may find complicated. In the discussion of various cardiovascular diseases, the personal approach is evident. The author stresses the importance of technical procedures, especially phonocardiography, which he believes is of increasing importance in cardiology. On the other hand, the important technical procedure of radiology of the heart in its various aspects might have been dealt with more fully. Nevertheless, although due recognition is given to graphic registration of cardiac phenomena, it is pleasing to note that some recognition is also accorded to the clinical study of the cardiac patient, and here and there criticisms can be raised at some of the statements that are made. For example, the vague term "præcordial pain" is used freely without any precise indication of the site of the pain. For instance, is it sternal, mammary, supra-mammary or infra-mammary? Again, discussing percussion, the author sums up: "Percussion is still a valuable method for recognition of the heart size and shape". It is questionable whether cardiologists in this country would accept this statement. Again, under rheumatic fever, "rheumatic polyarthritis" is noted, but there is no mention of the paper by Bywaters on the occasional occurrence of chronic post-rheumatic arthritis (Type Jacoud's) following rheumatic fever where the pathology is different from polyarthritis of the rheumatoid type. The statement that about half of the cases of rheumatoid arthritis reveal "rheumatic heart lesions" is certainly open to question, although rheumatoid nodules have indeed been discovered in relation to the pericardium, myocardium, endocardium and valves, &c. ("Rheumatoid heart disease"), in some cases of rheumatoid arthritis with nodules, that have come to autopsy.

There is an opening chapter on the history of cardiology and the historical approach receives recognition throughout the text. The bibliography is comprehensive and due recognition is given not only to American literature but also to British and European contributions to the subject. Throughout the text the reader is given many references to clinical pharmacology based on the author's researches in this subject. Certainly this book should be read by cardiologists and general physicians alike.

'Brit. Heart J., 1950, 12, 101.

Historical Review of British Obstetrics and Gynaecology 1800-1950. Edited by J. M. Munro Kerr, LL.D., M.D., F.R.F.P.S., F.R.C.O.G. (Hon.), R. W. Johnstone, C.B.E., LL.D., M.A., M.D., F.R.C.S. Ed., F.R.C.O.G., and Miles H. Phillips, Hon.M.D. (Bristol), M.B., B.S., F.R.C.S., F.R.C.O.G. (Pp. 420. 30s.) Edinburgh and London: E. & S. Livingstone Ltd. 1954.

The historical review of British Obstetrics and Gynaecology for the period 1800-1950 is a fitting sequel to H. R. Spencer's earlier work covering the preceding hundred and fifty years. The three editors, Professor Munro Kerr, Professor R. W. Johnstone and Professor Miles Phillips, together with 16 other contributors chosen from among the Senior Fellows of the Royal College of Obstetricians and Gynaecologists, with painstaking effort have helped to make it at once a remarkable historical contribution and a worthy gift to that Institute on the occasion of its semi-jubilee.

A study of the table of the contents immediately gives assurance of the systematic thoroughness that characterizes the book, three-quarters of which is devoted to the details of progress in obstetric practice while the remainder deals with the gynaecological advance. In the obstetric section each period of fifty years is generally reviewed. Thereafter special subjects are chosen for individual consideration by recognized experts and are dealt with in much greater detail. The gynaecological review is shorter but equally intensive and authoritative.

It becomes apparent that the period comprises both the dawn and the golden age of the specialty, for the history in describing the progress clearly shows how its art and science have evolved from humble beginnings practically to attain their zenith. In this achievement it provides the reader with essential and necessary perspective. It throws up in sharp relief the limitations under which the earlier generations practised their profession, with the equipment and knowledge made available in the last two or three decades. The absence of anaesthesia, especially to complicate the problems of uterine inertia and surgery, the grim spectre of unconquered puerperal infection with a mortality in excess of 10% on occasion; the imponderable problem of obstructed labour where no radiological diagnosis or safe relief by the lower segment operation offered itself; the non-existence of therapeutic transfusion; these and other handicaps were ever present and have been well drawn.

The evolution of the understanding of the aetiological problem and of the necessary techniques make most interesting and instructive reading, together with the advancement in physiological and pathological knowledge. Included amongst these are Braxton Hicks contractions, Hegar's sign,

concepts of the mode of natural separation of the placenta, the recognition of the lower uterine segment and its association with abnormal implantation of the placenta in antepartum hæmorrhage, the significance of this segment in obstructed labour and as an avenue of approach in Cesarean section, the mechanism of labour especially of Nägele's obliquity and Selheim's theory of lateral bending, the discovery of the sex hormones, and many other advances gradually emerge chronologically, as they influence the practice over the period under review.

Though emanating from the Continent the knowledge of the problems of sepsis really commences with Semmelweis' brilliant observation of the disproportionate incidence of infection in the two wards under his charge, tended in the one by midwives, where the mortality was low, and in the other by students, where the death-rate from infection exceeded 10%.

His concept of small particles originating in the post-mortem room proved to be a creditable anticipation of pathogens. The era of antiseptics merges into asepsis with its far greater security. Pen-pictures of the transition are delightfully drawn. The blood-spattered frock coat with turned back cuffs, greasy and grimy, appears as the veritable hall-mark of the operator in the earlier days. Braxton Hicks in setting down the various advantages of his manoeuvre of bipolar version states "we shall avoid (*inter alia*) the removal of the coat and baring the arm of the operator; and as a minor consideration [*sic*] the fatigue and pain endured by the operator while the hand is in the uterus".

Mr. Green-Armstrong amusingly recounts Wertheim's attitude towards asepsis in his protest against the wearing of rubber gloves condemning them as too modern and fashionable and interfering with the surgeon's *tactus eruditus*. The culmination in the fuller knowledge of the bacteriology of the hæmolytic streptococci and of the use of antibiotics in their control is clearly set out.

Many other techniques are traced through their varied stages of development. As instances may be cited the art of delivering the foetal head and the placenta, the control of post-partum and antepartum hæmorrhage, and the management of contracted pelvis.

The gradual transition of the specialist can be traced back to his occupation of a despised status, through the then privileged position in training of being allowed "to touch" certain patients until he emerges now carefully instructed and critically assessed in the role of a junior consultant. The earlier years in between were characterized by an extreme shortage of the needful clinical material, chiefly brought about by the greater safety of domiciliary midwifery and the surgical limitations imposed by the absence of anaesthesia and the fell scourge of sepsis.

The great strides in the reduction of foetal and maternal mortality are revealing and are a brilliant feature of the history. So are the undreamed of advances in gynæcological surgery.

This history helps to serve a further purpose. Each contribution offers an insight into the personality and the equipment of its author and the book as a whole reflects the gynæcologist of to-day.

Not least worthy of mention is the gradual emergence of the Royal College and of its Journal, in this history. The earliest beginnings may be discernible in the post-prandial trials of inhalation anaesthesia around Sir D. Y. Cameron's table, where a coterie of the elect collected to advance the art and science of the specialty.

This book, a gift to the College on its semi-jubilee, made possible through the generosity of Messrs. E. and S. Livingstone, the publishers, must be read by both practitioner and consultant, for its educative, instructive and historical value is high indeed. Its passages are frequently greatly entertaining and amusing as well. It conducts the reader to the hilltop of 1950 and the earlier valleys stand out clearly below. The pathway of ascent proclaims the uphill task and the coign of vantage now attained offers delicious relaxation when the journeying is leisurely surveyed.

Hypertension and Nephritis. By Arthur M. Fishberg, M.D. 5th edition. (Pp. i+196; 49 illustrations. 100s.) London: Baillière, Tindall and Cox Ltd. 1954.

This is one of the most important publications written in English on Hypertension and Nephritis. It embraces every aspect of the two subjects and reveals the author not only as an accurate observer but also as a profound thinker. It is not possible within the limits of a review to give a full account of the author's interpretation of all the changes which occur in hypertension; suffice it that the heart, arteries, nervous system, kidneys, endocrine organs, eyes, the blood and state of nutrition are each fully discussed. Treatment is exhaustively considered from every angle. There are separate chapters on general management and diet, pharmacological treatment and surgical measures. The latter include accounts of extensive sympathectomy, adrenalectomy and operations on the kidney. There is a brief reference to what the author terms psycho-surgery, that is, prefrontal leucotomy, in the hope of helping the hypertensive disease through elimination of emotional tension. It is doubtful whether the recommendation of an operation of this nature for the relief of high blood pressure will be favourably received. The author does not seem to have any enthusiasm for it. The swing towards treatment by surgery has in no way increased our knowledge of the nature of essential hypertension. Uræmia is dealt with in much detail. It is emphasized that treatment has become more successful since the clinical application of measurements of renal blood flow, glomerular filtration and some of the tubular functions of the kidney in Bright's disease. There is an excellent chapter on the toxæmia of pregnancy. The bibliography is extensive. As evidence of the success of this book it has now reached its fifth edition. It should be read by all practitioners interested, and who is not, in hypertension and nephritis.

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Section of Proctology

President—E. G. MUIR, M.S., F.R.C.S.

[November 10, 1954]

Rectal Prolapse

PRESIDENT'S ADDRESS

By E. G. MUIR, M.S., F.R.C.S.

It may be supposed that rectal prolapse is one of the prices man has had to pay for assuming the erect posture but it is by no means confined to him: it also occurs in the horse, dog and pig. Because of its obvious signs, it has attracted the attention of the surgeon from ancient days. Ambroise Paré cites the advice given by Hippocrates in difficult cases, where the prolapse could not be reduced, that "the Patient, hanging by his heels, be shaken, for so the gut by that shaking will return to its place".

John of Arderne, the fourteenth century English surgeon, whose life was so brilliantly portrayed for us by our Past President (Millar, 1954), naturally did not neglect the subject and quotes a royal case cured by his methods.

Of the early accounts, that given by Ambroise Paré in an English translation of 1634 is particularly interesting. In a short chapter entitled "Of the falling down of the Fundament", he says:

"When the muscle called the sphincter which ingirts the Fundament is relaxed, then it comes to pass that it cannot sustain the right gut. This disease is very frequent to children by reason of the too much humidity of the belly: which falling downe upon that muscle molesteth and relaxeth it or presseth it down by an unaccustomed weight, so the muscles called Levator Ani or the lifters up of the Fundament are not sufficient to beare up any longer. A great bloody flux gives occasion to this effect. A strong endeavour to expell hard Excrements, the Hæmorrhoids, which suppressed doe over-loade the right gut but flowing relaxe it: Cold as in those which goe without breeches in winter, or sit a long time upon a cold stone, a stroke or fall upon the Holy-bone: a palsie of nerves which goe from the Holy-bone to the Muscles the lifters up of the Fundament: the weight of the stone being in the bladder."

It is in many ways a typical Paré statement: the shrewd observations of a great man, mixed with some of the mediæval nonsense of the time. It is some four hundred years since Paré wrote his account and recently our attention was once again drawn to the part which injury to the nerves "which goe from the Holy-bone" may play in rectal prolapse, when Butler (1954) described 2 cases following operations upon the cauda equina.

Thomas Vicary (1626), of Royal College of Surgeons fame, wrote a book with the charming title of "The Englishman's Treasure". In this he states: "*A remedie for falling out of the fundament*. First beware of taking cold in that place and beware of costiffnesse, and keepe the Arse and Buttocks warm, and sit not on the cold Earth, nor upon stone or stones, nor upon any hard thing, but take somewhat under the buttocks: not only for falling out of the Longation or Arsegut, but for all other infirmities that may be in the Longation engendered."

In 1617 John Woodall, Master in Chirurgery, published his "Surgion's Mate, or a Treatise discovering faithfully and plainely the due contents of the Surgion's Chest, the uses of the Instruments, the virtues and operations of the Medicines, the cure of the most frequent diseases at Sea". One of these diseases was "Exitus ani or the falling down of the Fundament". Woodall's book was intended for "Young Sea Surgions employed in the East India Companies affaires" and he gives careful and practical instructions on the reduction of a rectal prolapse. In difficult cases the surgeon was first to "bestrew the gut fallen downe with Album Græcum well powdered and fine for this is precious though a homely medicine". Care was to be taken over the powdering for Album Græcum is stated to be "often full of sharpe pieces of bones very dangerous".

One's interest is naturally excited by the description: what could be the composition of "Greek White"? Fortunately a clue to its nature is given elsewhere in Woodall's book (Fig. 1). It does not need a classicist to see that it is, in fact, dog's dung. This substance is not naturally white but it will become white if the dog is fed on bones. The drug is obviously regarded as important and before setting out on a long sea voyage in those days, the surgeon either laid in a large supply of Album Græcum or alternatively took with him a large dog and a plentiful supply of bones.

As one might expect from one who was Serjeant Surgeon to King Charles II, a rather more sophisticated account of the condition was given by Richard Wiseman in 1676. After reduction of the prolapse he gives careful instructions to prevent recurrence. The patient should have "a couple of sticks whittled and fitted for him to place close on each side the *Podex*, so as in straining the Excrements may pass out, yet the Prolapse of the Intestine be hindred. For the like purpose I have frequently commended a small Tin-hoop to be fastened in a quilted Boulster, which being fitted with Bandage,

may be retained at that time to pass the Excrements through, and prevent the Relapse. What you can invent to this purpose will much facilitate the Cure".

Frederick Salmon, the founder of St. Mark's Hospital, wrote on rectal prolapse. He was born in 1796 and educated at St. Bartholomew's Hospital. He was appointed surgeon to the General Dispensary in Aldersgate Street and there developed his interest in rectal surgery. In 1835 he founded the forerunner of St. Mark's Hospital, by opening an infirmary called "The Infirmary for the Relief of the Poor Afflicted with Fistula and Other Diseases of the Rectum". In 1831 he published his "Practical Observations on Prolapsus of the Rectum".

One gets the impression that rectal prolapse was more common in his day and, further, that there was a certain social distinction about the disease. When discussing the causes of the condition, he states:

"Another common source of the disease is sedentary employments, through which the biliary secretion becomes scanty and a torpid state of the alimentary canal is induced. Persons thus occupied are too apt to indulge in the luxurious habit of sitting upon cushioned chairs, sofas, or stuffed seats. I have attended many cases of prolapsus among gentlemen of the legal profession, which I am certain were referable to this cause only; and to the same source may be traced its prevalence among females of all ranks, and in the higher grades of society generally."

After discussing conservative methods in treatment, Salmon describes excision, the first stage of which consisted in passing two large pins through the prolapse to fix it in position (Fig. 2). The

Album gracum.

S*tercus caninum, seu album gracum*, is hot and astringent, staith the laske, cureth the Squinancie, helpeth the Difenteria, and driueth away feuers that come by course, and is very good to strew the fundament fallen wichall, for it cureth the slipperinesse thereof, and caufeth it being gently put vp to stay vp, and being mixed and boyled with faller oyle to the thickenesse of an vnguent, is very good to cure the painefull Hemorroydes.

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FIG. 1.—The uses of Album Gracum by John Woodall (1617).

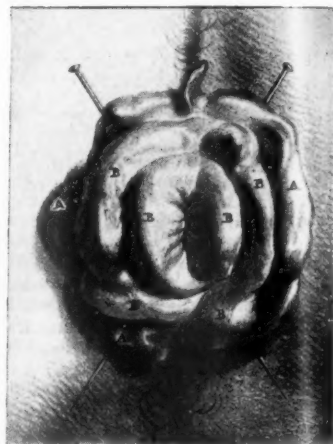


FIG. 2.—Rectal prolapse with transfixing pins in position, the first step in Salmon's operation for prolapse. A. The elongated portion of the mucous membrane around the inner margin of the sphincter. B. The columns of the rectum, enlarged by disease. (Reproduced from Salmon, 1831, Pl. I.)

pain produced by this part of the operation is described as "insignificant". He then excised the mucous part of the prolapse but was careful not to injure the muscle. The pins were left in position for an hour or two, after which the rectum was dressed with "sweet oil" and replaced.

The first classical account of rectal prolapse is that given by Alexis Moschowitz in 1912. He stated that at the point where the rectum left the abdominal cavity, there was a naturally weak point in the transversalis or pelvic fascia: that factors causing an increase in intra-abdominal pressure drove the peritoneum into the sheath formed by the outward prolongation of the pelvic fascia: that the anterior wall of the rectum was next indented and, the pressure continuing, the path of least resistance to the herniation was the anal orifice, through which the anterior wall of the rectum now appeared, followed by the complete ring. Stressing the fact that it was a hernia, his operation aimed at obliterating the hernial sac.

Moschowitz's operation has remained the model for many subsequent surgical experiments. He laid particular stress on the pelvic fascia and did not consider that the levator ani played much part in the production of rectal prolapse.

Treatment of the rectal prolapse by perineal amputation was popularized by Miles in 1933 and

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called rectosigmoidectomy. It is perhaps pertinent to quote Miles' own words regarding the level of amputation:

"The object of commencing this incision half an inch from Hilton's line is to prevent damage to the sphincters and especially to the points of fusion between the levator ani and the external muscular coat of the rectum, upon which depends subsequent control over the contents of the bowel."

Miles quoted 31 cases with 1 death and 1 recurrence and the operation became a popular one.

In 1942 Graham reported a further transabdominal operation for rectal prolapse. After division of the peritoneum in the pouch of Douglas, the inner edges of the two levator ani muscles were identified and they were then sutured together with interrupted silk sutures in front of the rectum, which was again sutured on either side to the levators. Other operations were: Lockhart-Mummery's (1910) operation of posterior rectal fixation performed by packing the pre-sacral space; McCann's (1928) performed through a perineal incision, in which the anterior fibres of the external sphincter were tightened and the two levator ani muscles brought together by sutures between the rectum and the vagina; sigmoidopexy, when the sigmoid colon was drawn up taut and fixed in the left iliac fossa; and innumerable combinations of different operations.

It is necessary to make some attempt to assess the results and no better beginning could be made than to consider next the discussion held by this Section five years ago on rectal prolapse (*Proceedings*, 1949, 42, 1005). I believe that the account of this meeting undoubtedly constitutes one of the most important papers ever published on this subject and those who contributed to it have every reason to be congratulated on the result. It was important partly for the wide range covered by the speakers: we were introduced to a religious sect in East Prussia who produce prolapse of the rectum upon themselves by straining at a religious rite; and partly for the unique contribution to the subject in a report by Hughes (1949) and Thompson (1949) on the work of St. Mark's Hospital upon no fewer than 215 cases of complete rectal prolapse in adults.

It was confirmed that rectal prolapse is much more common in women than in men, in the proportion of 6:1; that it tends to occur in men at an earlier age and that functional or organic disease and childbirth do not appear to be predisposing factors. Dickson Wright (1949) claimed that he had been able to discover more than 50 different procedures recommended for this condition, that 36 had been extensively employed and that 5 were in general use. The St. Mark's figures (Hughes, 1949) gave the results of a number of different operative procedures; in general, the mortality rate was very low and the recurrence rate very high but more detailed consideration is required:

Lockhart-Mummery's operation.—Of 30 traced cases, 1 had died and 29 had recurred.

McCann's operation.—This had been performed on three occasions but all had recurred.

Sigmoidopexy.—In 8 traced cases all had recurred, though 2 had also been combined with obliteration of the pouch of Douglas, presumably in the style of Moschowitz.

Moschowitz's operation.—Of 6 traced cases, 1 died, 4 recurred and 1 was successful. An additional Moschowitz was combined with suture of the levator muscles and this case was successful.

In 1952, Brintall, when advocating a combined abdominal and perineal approach for rectal prolapse, also reported 12 cases treated by Moschowitz's operation, with 8 recurrences out of 11 patients traced.

It seems fair to say that on the evidence presented, these four operations—Lockhart-Mummery's posterior proctopexy, McCann's operation, sigmoidopexy and Moschowitz's operation—are ineffectual in the treatment of rectal prolapse and that the occasional success does not justify their continued use.

RECTOSIGMOIDECTOMY

The largest number of cases from St. Mark's Hospital had been treated by the operation of rectosigmoidectomy and the results were most ably reviewed by Hughes and Thompson. The operation had been performed in 150 cases without operative mortality and of these 108 had been traced. 65 (60%) had recurred and 43 (40%) had not recurred. Most of those who had recurred were incontinent and it was the author's opinion that when the operation failed to cure the prolapse, it often made the patient incontinent when some continence had existed before the operation. Of the 43 patients in whom the prolapse had not recurred, no less than 21 were incontinent in varying degree. Only 15 (14%) patients had very good results and of these 50% were males. These figures make depressing reading. Further, it should be remembered that these results were obtained at St. Mark's. At some hospitals both the mortality of the operation and its after-results might have been worse, though the criteria of success might not be so severe.

Other writers have given a more cheerful picture of rectosigmoidectomy. Miles, in his original report, quoted 31 operations with one death and one recurrence and stated "sphincter control gradually improves and at the end of six months, or less, is usually fully restored". Gabriel (1948) reported 64 cases with 2 deaths. Of 38 traced cases operated upon, more than two years before, 30 had had an excellent result, 3 had improved and in 5 the prolapse had recurred. Of these (all women) 1 was mentally dull, 3 were senile and frail and 1 relapsed after two years, owing to very heavy domestic duties.

These reports are somewhat conflicting. It is certain that all proctologists must have made some

use of the operation of rectosigmoidectomy and no doubt one's views are coloured by personal experience. I think it is fair comment on the operation to say that:

(1) On theoretical and practical grounds it has little chance of providing a real cure for rectal prolapse. It is true that the prolapse is resected but the resection is performed in the perineum, outside the anus, and then replaced. With the best will in the world (and Miles gave careful instruction in his original paper on pulling down the sigmoid colon), it is difficult or impossible to remove all the "slack" of the bowel. It is advised that in rectosigmoidectomy the peritoneum in the pouch of Douglas should be closed at a higher level but when we consider the usual abdominal appearance of the pelvis in a typical case of complete rectal prolapse, it is certain that no material alteration can be made from the perineal route. Thompson describes watching through a laparotomy incision the peritoneal suture being inserted by a surgeon performing a rectosigmoidectomy and states that any alteration in the size of the peritoneal pouch was negligible in comparison to its total size. In the standard operation of rectosigmoidectomy, no attempt was made to repair the pelvic floor but others have added this to the operation and Gabriel considers that suturing the adjacent edges of the puborectalis muscles together, after closing the peritoneum, is of practical benefit.

(2) The frequency of incontinence after rectosigmoidectomy, at least in the St. Mark's series, is very high. Patients with complete rectal prolapse are seldom fully continent, though, considering the grossly overstretched anal sphincter, the degree of continence they possess is often surprising. Lloyd-Davies (1949) attributes this to sensations derived from the pelvic floor. Hughes and Thompson did not state, and probably could not discover in a follow-up of this kind, the exact degree of incontinence in their patients prior to the operation but they definitely infer that, whether the prolapse was cured or not, many patients subjected to the operation were made incontinent, or more incontinent than they were before.

It is the experience of surgeons who use the operation of anterior resection, or the occasional abdomino-anal resection, in the treatment of rectal cancer, that if the line of resection is very low in the rectal ampulla, there may be some interference with normal continence, whether temporary or slight. The work of Gaston (1948) and Goligher (1951) has suggested that the preservation of perhaps $1\frac{1}{2}$ in. of rectal ampulla is desirable to ensure normal continence and in these cases there is a normal functioning sphincter.

In rectosigmoidectomy, Miles advised making the incision for resection $\frac{1}{2}$ in. distal to Hilton's white line and though this is not a very accurate marking (Ewing, 1954) it is obvious that after a resection performed in this manner, almost no rectal ampulla can remain. In these cases we are not dealing with a normal sphincter but with an already over-stretched and inefficient one and Goligher believes that the poor results are due both to the hypotonic sphincter and the small piece of ano-rectal mucosa.

The usual rectosigmoidectomy does damage to some extent the mechanism of normal continence and it is perhaps surprising that a patient can preserve continence after this operation: it shows that we cannot lay down rules for all patients. Nevertheless, it would seem desirable that when the operation is performed, the line of resection should start $2\frac{1}{2}$ in. to 3 in. from the anal margin and thus preserve more of the ampulla. Even if this slightly increases the recurrence rate, it will be well worth while if it reduces the incontinence rate.

(3) The most important features in the operation of rectosigmoidectomy are that its mortality is very low and that it removes the offending prolapse. It is true that at the present time modern anaesthesia and antibiotics have done much to lessen the risk of an abdominal operation but there are a number of cases of complete rectal prolapse where the patient's general condition is such as to make an abdominal operation unjustifiable.

My last case of rectosigmoidectomy was performed on an octogenarian with complete rectal prolapse. Unfitted for an abdominal operation, she stood a rectosigmoidectomy without anxiety and left the hospital happily, with continence, to enjoy her remaining years. There is no other operation which could have given her the same relief with the same degree of safety and I am quite prepared to repeat the operation if and when the prolapse recurs.

We should be very wrong in condemning rectosigmoidectomy, though I believe it should be reserved for patients unfit for an abdominal operation and it must leave an adequate rectal stump.

PARTIAL PROLAPSE WITH ANAL INCONTINENCE

It would be a deliberate simplification of the problem to consider anal incontinence only in relation to complete rectal prolapse, for many troublesome cases in elderly women have only mucosal prolapse with a very relaxed sphincter. Digital examination shows a patulous anus and an almost complete absence of tone in the sphincter. For this reason, the anal canal is shortened and rectal mucosa seems to reach the anal margin. These cases, like complete prolapse, seldom seem to be associated with perineal or pelvic floor injury: many of them are found in elderly unmarried women. Nor does the condition appear to be a stage in the development of a complete rectal prolapse. The primary complaint of these patients is usually of incontinence and not of prolapse. In a fair proportion of cases of complete prolapse, the patient is continent provided the prolapse is not down. Gabriel

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considers the condition to be one of fatigue and exhaustion, which may be caused by the excessive and longstanding use of purgatives. Whatever the cause, there must be some factor which prevents most of these patients from developing a complete rectal prolapse and yet allows a complete prolapse to develop in other patients, sometimes with considerably more sphincter tone. Amongst these patients are found the rectal neurotics, sometimes so confused by their anal musculature that they can no longer distinguish between contraction and straining.

Incontinence caused by perineal or obstetric injury clearly calls for gynaecological treatment and perineorrhaphy. For other cases a number of different surgical operations have been described, in which the sphincter is tightened or fibres of the gluteus maximus brought in to replace it. I have no personal experience of these plastic operations and have only used submucous carbolic oil injections, sphincter exercises with electrical stimulation and Thiersch's operation. I believe the majority of these cases can be benefited though not cured by these measures and they are without much risk to the patient. Gabriel and Dickson Wright have both reported favourably on Thiersch's operation, the latter using it as an 8-shaped silver wire loop for combined procidentia of uterus and rectum. I regard it as a very useful procedure but at least 30% of my cases have required the removal of the wire.

COMPLETE RECTAL PROLAPSE

Etiology

It is much more common in children than adults and has been attributed to causes ranging from absence of the sacral curve and loss of perirectal fat in wasting diseases to ill-disciplined straining at stool. It was apparently not uncommon in concentration camps and here starvation, absence of retroperitoneal and perirectal fat, muscular weakness and dysentery all played their part. These factors do not arise in ordinary civil life.

The majority of cases in children do well on conservative lines, and I have found no evidence to suggest that there is a tendency for them to recur in old age. I propose to confine myself to complete prolapse in adults. What are the factors which retain the rectum in its normal position and by their fault or failure permit prolapse?

The Peritoneum and Subperitoneal Connective Tissue

By means of the peritoneum and subperitoneal connective and fatty tissue the rectum is held against the sacrum and follows the concavity of that bone. We know from operative interference that the attachment is usually firm and the part it normally plays in retaining the position of the rectum against gravity and the alterations of intra-abdominal tension must be important. In the typical case of complete rectal prolapse in a female, the rectum is usually found to have almost complete peritoneal investment like the sigmoid down to the sacrococcygeal junction (Figs. 3 and 4). The mesorectum

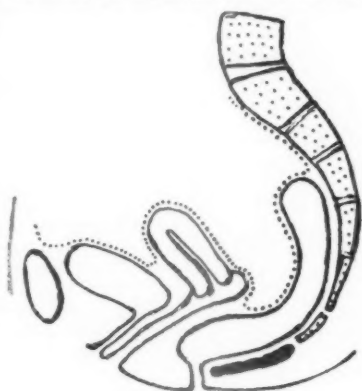


FIG. 3

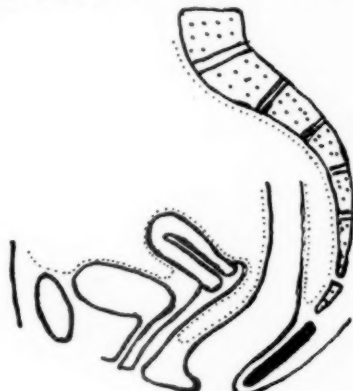


FIG. 4

FIGS. 3 and 4.—The pelvic peritoneal investment in the normal female and that usually found in complete rectal prolapse.

may be an inch or two in length and its attachment is usually to the left side of the pelvis, near the sacrum, but even this attachment seems loose and can be moved from side to side. The sacral concavity is smoothly covered by peritoneum and looks surprisingly bare. If the prolapse is not down here is a good deal of rectal "slack" in the pelvis. At the sacrococcygeal junction the peritoneum passes off the rectum on to the surface of the two levators but the rectum is still loose and in some cases can be lifted up almost to the levator hiatus. There are no rectal stalks or they are smaller than normal. Anteriorly there is a deep pouch of Douglas, the posterior vaginal wall being covered



FIG. 5.—The normal position of the rectum following the sacral curve demonstrated by a barium enema in the knee-elbow position.



FIG. 6.—Rectum outlined by barium in a normal female in the erect position demonstrating its adherence to the sacral curve and the almost horizontal position of the rectum from the coccyx forwards to the anal canal.

by peritoneum almost down to the levators and there is therefore very little of the rectovaginal septum. The perineal body is small but in the inch or two where the rectum is in contact with the posterior vaginal wall I have usually found its attachment to be normal. Pressure on the anterior rectal wall in the pouch of Douglas will cause it to prolapse through the anus, separating the two puborectalis muscles and passing through the dilated sphincter. I have found no significant alteration in the vascular arrangements; the inferior mesenteric pedicle is naturally loose when the prolapse is up and taut when it is down but the middle hæmorrhoidal arteries appeared little more than normal in length when they were identified. These peritoneal arrangements in the pelvis are almost constant in complete rectal prolapse and can be demonstrated by a small barium enema with X-rays taken in the knee-elbow and standing positions. With some variations the normal rectum follows the curve of the sacrum and this is well shown in both positions (Fig. 5 and 6). In a case of complete rectal prolapse with the rectum reduced, the knee-elbow film shows it fallen away from the sacrum and in some cases passing directly upwards from the anus with a curve almost concave towards the sacrum (Fig. 7). In the standing position the rectum lies in a tumbled heap at the bottom of the pelvic cavity with the rectosigmoid junction opposite the sacrococcygeal region (Fig. 8). The pelvic peritoneum is stated to extend much lower in infancy than in adult life and in certain animals such as the dog a complete peritoneal investment of the rectum is normal. In the adult with a complete rectal prolapse the unusual peritoneal arrangement might either be due to the drag of the prolapse or a predisposing cause. I prefer the latter view. I think that a peritoneal arrangement of this type is probably a congenital abnormality though with recurring prolapse it would naturally become much more pronounced. The rectum passes in a direct line downwards to the levator hiatus, with a mesentery but without the usual sacral curve and if in such a case levator weakness or persistent stress is present prolapse might easily occur.

The Lateral Ligaments of the Rectum and Pelvic Fascia

It is generally believed that the rectum is also held in its place by the lateral ligaments or rectal stalks. These are said to be thickenings of the pelvic fascia and connective tissue around the middle hæmorrhoidal arteries as they pass from the side walls of the pelvis to the rectum. With them, in addition, are venous channels, lymphatics, sympathetic nerve fibres, and fatty tissue.

In 1953, Berglas and Rubin cut large sagittal and coronal sections of the female pelvis after injecting the blood vessels in cadavers and submitted the sections to histological examination. It was their conclusion that sheath-like condensations of connective tissue around the pelvic organs designated as fascia do not exist and that the bulk of tissue structures erroneously taken for ligaments consist of plexuses of blood vessels, particularly venous, in loose connective tissue: that the pelvic connective tissue has no firm attachment to the pelvic walls or fascia covering the levator ani muscles but is simply continuous with the retroperitoneal tissue: that there is no evidence that the pelvic organs

FIG. 7.—Rectum and sigmoid colon suffering from complete prolapse from the coccyx forwards to the anal canal.

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FIG. 7.—Film in the knee-elbow position of the rectum and vagina outlined by barium in a patient suffering from complete rectal prolapse. (Tip of coccyx marked.) The rectum is widely separated from the sacrococcygeal curve.



FIG. 8.—Film in the erect position of a barium enema in a patient with complete rectal prolapse. The rectum turns forward away from the sacrococcygeal curve at the level of the sacrococcygeal junction. The direction of the rectum, and therefore that of the levator raphe, from the tip of the coccyx (marked) to the anal canal appears almost vertical. For comparison with the normal in Fig. 6, though there is some pelvic tilting.

are supported by connective tissue structures or blood vessels and that their real support is an intact muscular pelvic floor, capable of varying its tension with the constant variations of intra-abdominal pressure. Other writers have expressed somewhat similar views and no doubt future work will confirm or refute their statements. Their work was primarily an investigation of uterine support but its implications on the rectum are obvious.

Surgically the rectum appears to be tethered to the side wall of the pelvis by the rectal stalks. Anteriorly it is adherent to the greater part of the posterior vaginal wall forming the rectovaginal septum on either side of which are the uterosacral ligaments. No doubt these structures are only composed of arteries, venous channels and connective tissue but they certainly seem to play a part in the fixation of the rectum. It is possible that their support would be insufficient without a strong pelvic floor but in cases of complete rectal prolapse they are either absent or of insignificant size.

I have never found it easy to accept the layers of pelvic fascia which are said to intervene between the different organs in the pelvis. I have not identified them myself nor seen them convincingly displayed by others and it is a relief to read of someone denying their existence. The fascia of Waldeyer is a different matter. It can be seen, felt and cut. Passing forward from just above the sacrococcygeal junction, it is attached to the rectum at the anorectal ring and so assists in supporting it from the posterior and posterolateral walls. Anterolateral to the levator hiatus it is very thin and it is difficult to accept operations which aim at strengthening the pelvic floor in this region by suturing this material. If the evidence is accepted the fascia of Waldeyer, covering the surface of the levator ani, is the only true fascia in the pelvis. It assists in the attachment of the rectum to the levator hiatus. Any damage which it sustained here would almost certainly be associated with levator damage and though fascial weakness has often been suggested as a cause of prolapse the muscular part of the pelvic floor is probably much more important.

The Levator Ani Muscle

No one can doubt the importance of this muscle in rectal prolapse. The work of Milligan and Morgan (1934) in this country and Courtney (1950) in the United States has done much to assist us in its structure and function. Certain features are pertinent to rectal prolapse.

As the rectum reaches the hiatus in the levator muscle its longitudinal muscle gives off fibres which fuse with the levator fascia (fascia of Waldeyer) and the superficial fibres of the iliococcygeus and pubococcygeus muscles to form a Y-shaped layer of muscle, the iliorectococcygeous, which surrounds the rectum laterally and posteriorly and passes backwards to be inserted into the anterior surface of the coccyx and lower sacral segments (Courtney).

The deep part of the external sphincter is intimately related to the puborectalis muscle and with the

longitudinal muscle of the rectum and the internal sphincter forms the anorectal ring (Milligan and Morgan).

Although the rectum lies on the levator plate or raphe between the coccyx and the anus with the fascia of Waldeyer intervening, it is at the hiatus that it is firmly attached to the fascia and muscle and more posteriorly than anteriorly. This attachment usually prevents the eversion of the anal canal and explains the groove present around the presenting rectal prolapse. Further the close attachment of the rectum at the hiatus suggests that weakness or injury would undoubtedly influence the development of prolapse.

Berglas and Rubin (1953) recently studied the function of the levator ani in relation to the pelvic viscera by X-ray myography. Using half-strength Rayopake, they injected the two puborectalis muscles through the lateral vaginal wall and the levator plate midway between the coccyx and the anus. With barium emulsion in the rectum and vagina the movements of muscle and viscera could be noted in different positions of posture and of strain. It was their view that in the erect position in the female with a normal pelvis the rectum lies almost horizontally upon the levator raphe or plate as it passes forwards to the anorectal junction, the vagina lies horizontally above the rectum and the cervix uteri is placed almost vertically above the coccyx. When straining occurs these organs are forced backwards against the levator and coccyx; there is no tendency for them to be forced down the levator hiatus. The levator plate is forced into a more oblique position and this depends on the strength and co-ordinated function of the muscle and probably most on the pubococcygeus and puborectalis portions. Myograms show that the levator hiatus is pulled forwards slightly on straining and that its posterior outline becomes more rounded (Figs. 9 and 10). If the strength or tone of the



FIG. 9.—Lc, levator crura; Lh, levator hiatus; Lp, levator plate.

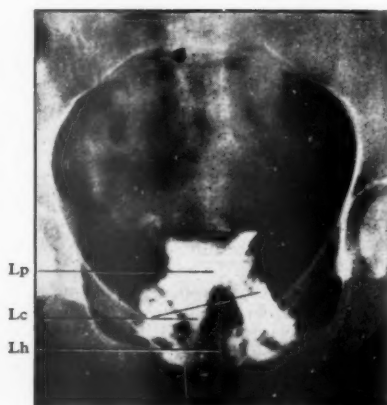


FIG. 10.—Lc, levator crura; Lh, levator hiatus; Lp, levator plate

FIGS. 9 and 10.—Myograms showing the appearance of the levator hiatus in the normal female in relaxation (Fig. 9) and straining (Fig. 10).

(Reproduced from Berglas and Rubin, 1953, by permission of the authors and of the Editor of *Surgery, Gynecology and Obstetrics*.)

levator has been diminished by any factor, such as birth injury, nervous disease or general weakness, the obliquity of the levator plate will be increased (Fig. 8). I think it is a matter of clinical observation that in elderly women with a weakened pelvic floor the anal orifice tends to drop downwards and backwards and the curve forwards from the sacrococcygeal region becomes less pronounced. Straining now produces still more obliquity of the levator plate and as this increases the pelvic organs come to lie still more directly over the levator hiatus. Eventually an increase in intra-abdominal pressure tends to force these organs through the levator hiatus which may not only have weakened walls but be enlarged in size through birth injury.

I have carried out levator myograms on a number of patients using diodone with Hyalase and making the injections through the ischiorectal fossa rather than the lateral vaginal walls. I think the latter route probably gives a clearer picture of the puborectalis muscle but it has obvious disadvantages. The pictures obtained of the levators in rectal prolapse (Figs. 11 and 12) appear very similar to those of Berglas and Rubin in uterine prolapse and it is interesting to speculate on the factors which determine which organ shall prolapse. I have assumed with very little evidence that birth injury to the levator and damage to the peroneal body are more likely to produce uterine prolapse while levator weakness with an abnormal peritoneal covering to the rectum and pelvic floor will tend

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FIG. 11



FIG. 12

FIGS. 11 and 12.—Myograms showing the appearance of the levator hiatus in a female suffering from complete rectal prolapse in relaxation (Fig. 11) and straining (Fig. 12). Even in relaxation the hiatus is enlarged and on straining with the descent of the prolapse the hiatus is stretched apart.

towards rectal prolapse. I do not wish to exaggerate the importance of levator myography. The findings are interesting but in fact are only what might reasonably be surmised. Further, there is no absolute assurance that the injected fluid will take up accurately the whole outline of the muscle and inferences from X-ray pictures might be unsound. Barium emulsion in the rectum alone will give most of the information obtained by a myogram. All the cases of complete rectal prolapse I have examined have shown in the erect position in relaxation an increase in the downward slope of that part of the rectum beyond the coccyx more than I should have expected in patients of their age. On straining this becomes more marked and as the prolapse descends the anus seems to lie almost vertically below the rectum, an impression which is somewhat increased by the flexion of the spine which the patient tends to adopt (Figs. 13, 14 and 15). Once prolapse has occurred its repetition still further stretches the hiatus and weakens the levator.



FIG. 13



FIG. 14



FIG. 15

FIGS. 13, 14 and 15.—Films taken in the erect position of a female suffering from complete rectal prolapse with rectum and vagina filled with barium. Before straining (Fig. 13), at the beginning of straining (Fig. 14) and with the rectum completely prolapsed (Fig. 15). The obliquity of the levator plate from the coccyx (marked) to the anal canal is well shown, also the anteroposterior compression of the vagina beginning in Fig. 14 and its flattening backwards in Fig. 15.

The Sacral Curve

It has been suggested that a diminished curve in the sacrum might play a part in prolapse but it is doubtful if evidence will ever be obtained to confirm or refute this. The effect of the levator on the forward curve beyond the coccyx has already been considered.

It is reasonable to assume that the important causes in the production of rectal prolapse are an abnormal peritoneal investment and a weak pelvic floor and that in the latter, muscular weakness is a much more important factor than fascial weakness. Both the peritoneal arrangement and the weak pelvic floor could be cited as cause or effect but I think it probable that while each separately might be insufficient, the combination would strongly predispose towards rectal prolapse. Surgical treatment must alter the peritoneal floor in the pelvis and strengthen or protect the levator ani. The first part can only be performed from the abdomen and I believe it is essential that the peritoneal floor should be taken up like an ill-fitting carpet and relaid over a levator ani protected against further shocks. Unless this is done, there can be no security. Moschowitz's operation aimed at obliterating the pouch of Douglas but this was done by intraperitoneal sutures. Peritoneum is notoriously fickle. It can form dense adhesions in some cases: in others, when the abdomen is opened a few months after an operation, hardly a scar remains. The best security for the rectum is for it to gain a firm attachment to the pelvic walls by fibrous tissue and intraperitoneal sutures alone cannot secure this.

ANTERIOR RESECTION IN THE TREATMENT OF RECTAL PROLAPSE

Six years ago I found it necessary to perform an abdominoperineal resection on a patient who had previously had an anterior resection. As might be expected, I found it extremely difficult to separate the site of the anastomosis from the sacrum and pelvic walls and it was necessary to cut it away with a knife. This was not due to invasion by growth, for the recurrence was a small one and the patient is alive six years later. It seemed to me that the firm adhesions around the site of anastomosis might make the operation of anterior resection a useful procedure for rectal prolapse and I have used it since on a number of cases.

The operation is the same as when performed for rectal cancer but in order to allow the rectum the opportunity to form fresh adhesions it must be fully separated in all cases down to the levator ani muscles and the levator raphe exposed. The dissection should display the junction of the rectum with the levator muscle and the peritoneum covering the posterior vaginal wall should be dissected up from its deepest level and removed. The rectum is now divided below a clamp, leaving an adequate rectal stump of some three inches on the stretch above the levator floor. The line of section has usually been in the region of or immediately below the peritoneal reflection on the anterior rectal wall. When the depth of the pouch of Douglas is considered in these cases, this may appear unduly low but the rectum is very loose and capacious and there has usually seemed to be a good deal more of it below the peritoneal reflection than might be expected. A suitable site on the sigmoid colon is selected, which will remove any unnecessary "slack" but avoid tension, and the anastomosis performed. When completed, the rectal stump passes backwards and upwards from the levator hiatus and the anastomotic ring lies in front of the left sacrococcygeal region and its angle with the left pelvic wall. As in an abdominoperineal, the peritoneum is stripped up from the side walls of the pelvis and as much as possible of the back of the broad ligaments and it is now sutured with the aim of securing:

(1) That the sigmoid shall pass through the new peritoneal floor on the left posterior side of the pelvis. This is its natural position to take up.

(2) That the uterus, broad ligaments and tubes shall fall backwards towards the sacrum, to the right of the sigmoid. Part of the pouch of Douglas has already been obliterated by stripping, and by sutures the uterus and tubes are brought against the peritoneum covering the front of the sacrum.

The ideal to be aimed at is that the plane of the peritoneum covering the sacral promontory shall pass downwards over the front of the uterus and broad ligaments (Fig. 16).



FIG. 16.—The position sought at the completion of the operation with the vagina and uterus fallen back on the right of the pelvis, the rectosigmoid anastomosis on the left and the peritoneal plane passing down over the front of the uterus and broad ligaments without a pouch of Douglas.

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At the conclusion of the operation a stab drain is introduced from the perineum into the presacral space.

This operation excises the prolapse and does so from above so that all sigmoid slack can be removed. It can leave a rectal stump of the desired size so that interference with normal continence does not occur. The anastomosis becomes firmly fixed to the sacrum and left wall of the pelvis and not only prevents prolapse but helps to protect the levator ani from strain (Fig. 17). The upper part of the



FIG. 17.—Post-operative film in the knee-elbow position of a patient with complete rectal prolapse treated by anterior resection.

vagina, the uterus, tubes and broad ligaments fill up the pelvic aperture on the right and mid-posterior parts; the sigmoid on the left. The peritoneal pelvic floor is stripped up and relaid with the opportunity to form fresh attachments. I do not think it likely that complete rectal prolapse could ever occur again after this operation. I use the word "complete" because it is possible for some mucosal prolapse to occur after an anterior resection.

I have now used this operation with success for complete rectal prolapse on 8 patients, all women, at ages ranging from 46 to 82. It has also been used on 3 other occasions by surgical colleagues. Since the longest post-operative period is only six years I am in no position to make extravagant claims but I believe the operation will cure prolapse and do so without residual disability. There has been no mortality and it has been my experience, and I know that of others, that anterior resection is an operation which elderly patients, especially women, stand extremely well.

In the immediate post-operative weeks all my patients have found some difficulty in controlling liquid faeces and considering the previously stretched state of their anal sphincter this is not surprising. They are given sphincter exercises and the anorectal ring recovers its tone sometimes quickly, sometimes in the course of the next few months, now that the constant stretching of the hiatus has been stopped. These patients are left with normal continence but 2 complained that they found some difficulty in forcing out the motion from the rectum and I have heard the same complaint after anterior resection for carcinoma.

I have made no attempt to suture the levators. A torn perineum would call for perineorrhaphy but this has not been present in any of my patients. The appearance of the levator ani muscles as seen from above does not suggest to me that sutures aimed at drawing the muscle fibres of the two levators together between the rectum and the vagina would be either anatomically correct or likely to remain in position.

I do not suggest that anterior resection is the only cure for rectal prolapse and there are two other operative procedures which require mention. Butler (1954) advises abdominal removal of the deep pouch of Douglas and complete mobilization of the rectum followed by perineal rectosigmoidectomy, suture of the colon to the side wall of the pelvis and ventrofixation of the uterus. Excellent results have been obtained. I prefer the resection to be performed from the abdomen and as regards ventrofixation, I think it better that the uterus should fall back after the operation than stay forwards though it is as well to remember that this organ sometimes shows an extraordinary disinclination to stay where it is put.

In 1949 Lloyd-Davies described an operation for complete rectal prolapse in which he placed six floss silk slings between the rectum and the vagina at different heights, tethering the slings posteriorly to the sacrospinous ligaments and forming a rectovaginal septum by uniting the anterior rectal wall to the back of the vagina by non-absorbable sutures. The operation was completed by obliterating the pelvic peritoneum at the sides of the rectum by other non-absorbable sutures in the method of Moschowitz. The results were excellent but I think the operation has been still further improved since the author now starts by freeing the rectum completely as for a resection and there are now opportunities for fresh retroperitoneal adhesions to form.

Complete rectal prolapse calls for an abdominal operation in which the deep pouch of Douglas must be excised, the pelvic peritoneum stripped up, the rectum mobilized and resected or otherwise fixed so that it can obtain a secure attachment to the pelvic walls. Where age or frailty make this impossible rectosigmoidectomy is a most useful operation. Thiersch's operation can be used for mild cases or the very infirm or sometimes combined with rectosigmoidectomy. Sphincter exercises are useful in all cases.

I have given something of the story of rectal prolapse and its treatment. There is much I have omitted and no doubt many of my assumptions will be refuted by the experience of others. "Flat and flexible truths are beat out by every hammer", said Sir Thomas Browne. No doubt he was right but after all, knowledge is gained from experience and experience is but trial and error.

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Section of Radiology

President—J. F. BROMLEY, O.B.E., F.R.C.P.

[October 15, 1954]

Reflections on Radiation Hazards in Clinical Practice

PRESIDENT'S ADDRESS

By J. F. BROMLEY, O.B.E., F.R.C.P.

THERE are two particular reasons at this time which make the subject of radiation hazards and protection important to radiologists. First, we have a duty to our staff, to ensure that their working conditions are safe in daily clinical practice. I am not thinking of medico-legal embarrassments but of our plain duty to provide secure proper conditions of work, and to make sure that these are effective by reason of being understood and applied intelligently.

My second reason for believing that we must interest ourselves as perhaps never before in problems of protection is the conviction that it is properly to the radiologist that society ought to look for enlightenment of present misgivings and fears resulting from the publicity given to the whole subject of artificial radio-activity, with all its related consequences. The radiologist, for many years the pioneer in applying clinically these "ionizing radiations" (how much more dreadful they sound under that name) must take the lead in interpreting, in trying to "humanize" this new thing to a puzzled and harassed world. The fact that a particular quantity of radiation is *detectable* by the sensitive tests of modern chemical and physical agents does not necessarily mean that it is lethal, or even injurious.

Radiation hazards and injuries to the skin were the first of the injurious effects by the rays to be recognized, and have been the subject of innumerable communications ever since; Sievert (1947) tentatively suggested that the safety *skin* tolerance dose might be of the order of 0.1 to 0.5 roentgen per day. I have been at some pains to discover the earliest clinical account of skin injury. The following appeared in the *British Medical Journal* six months after Roentgen's announcement of his discovery. A Dr. Stevens (April 1896) writes:

"A gentleman who had been assiduously experimenting with the Roentgen rays ever since the announcement of their discovery, and who has been working chiefly with the cryptoscope, called attention to the condition of his skin. The upper and lower eyelids of both eyes, the *ala nasi* and the upper lip were all swollen and the seat of an erythema which was not itchy but very painful. The affection was also on the hands and wrists and on the prepuce. On the back of the hands were some raised and hard spots. There was no constitutional disturbance. This and the seat of the eruption point conclusively to irritation as the cause."

The Editorial comment is: "These facts have been observed before, but their true interpretation is perhaps a little different from the conclusions arrived at by our correspondent . . . it seems probable that the observed rash is more in the nature of a sunburn."

The first of that long line of alarmists who have since added their quota of trouble to X-ray departments was probably that correspondent to *Nature* (? Turner, 1896) who after describing some simple fluoroscopic experiments adds ominously "the hand appears to feel a cold sensation under the rays". Patients (and staff too for that matter) have since been all too readily disposed to follow the trail blazed by this pioneer.

Hazards connected with the blood and the particular vulnerability of lymphocytes and lymphatic tissue have likewise been familiar to radiologists since the early years of the century (Heineke, 1904; Bythell and Barclay, 1912): that some uncertainty about details, however, still tends to prevail in hæmatological circles, is suggested by disconcerting types of report, after this fashion (in this case for a theatre nurse):

"No gross abnormality noted in red cells or platelets. This nurse's blood shows rather low values for the red cell count and hæmoglobin. There is a relative lymphocytosis, but the absolute count of lymphocytes is not abnormal. On the whole I would not regard this as a satisfactory count for a person exposed to a radium hazard, since the red cell count and the hæmoglobin levels offer little margin of safety."

I quote this fairly typical specimen only to illustrate the real difficulty that can arise even when the hæmatologist is fully conscious of his responsibility, anxious to face up to it, and genuinely wants to be helpful.

New red blood cells and granulocytes both originate from reticulum cells of the bone-marrow, but while the red cell has an expectation of life of about four months, the granulocyte can only look forward to some three or four days, and the lymphocyte (arising from lymph glands and lymphoid tissue generally) to not more than twenty-four hours, or even less. If therefore the blood and lymphocyte-forming tissues are exposed to radiations (particularly to doses which are going to be harmful) the effect, as expressed in the blood picture, will become manifest in "patches" or "breaks"

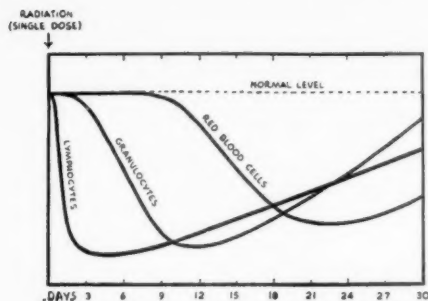


FIG. 1.—Effect on blood counts of a single total body exposure of the order of 500 r (Spear, 1953). By kind permission.

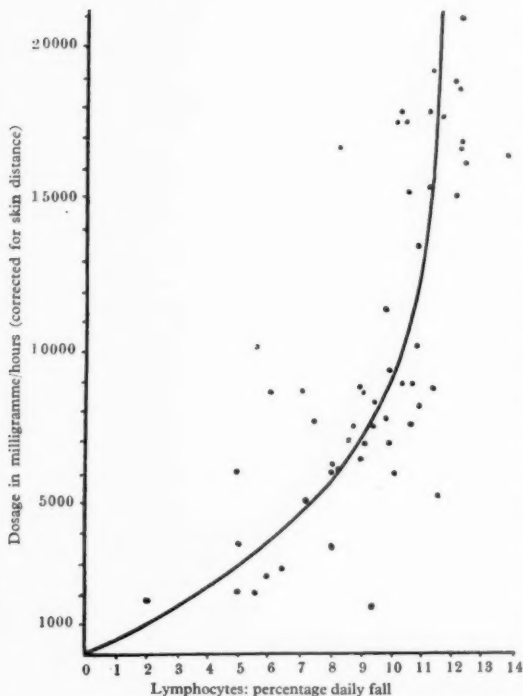


FIG. 2.—Daily percentage lymphocyte fall related to radiation dosage (Goodfellow, D. R., 1936, *Acta radiol.*, Stockh., 17, 35).

A radiographer (a girl aged 22) joined the staff one April, with an apparently satisfactory blood count, which then fell consistently over the next three months, and even after eight months (during which the hæmatologist's reports became increasingly lyrical) was still ranging between 3,600 and 4,000 total white cells, of which rather less than 2,000 were granulocytes, though with 1,500 to 2,000 lymphocytes. She changed her occupation, and for three months after leaving, her blood count showed a steady rise, but sustained another fall during the following April and May (before her marriage), after which it rose again, until March this year, when it fell yet again—an interesting (and apparently rhythmical) variation (Fig. 3). I should add that at no time did her test film show evidence of excessive exposure to radiation.

corresponding to the life-circle of different types of cell (Fig. 1). But this is to over-simplify. Let us suppose that these exposures are fairly small (as may well happen to persons who work in a chronic radiation risk) but are continually repeated; that doses may be small enough to injure cells while permitting subsequent (if temporary) over-production by parent tissues; while these parent tissues themselves may have different recuperative powers—it is surely obvious that the difficulties of interpreting a single haphazard blood count must be such as to deter the most imaginative hæmatologist. Moreover I still have in reserve the suggestion by Mottram (1931) that the more highly penetrating radiations (such as gamma rays of radium) may manifest their action first and most constantly as one on bone-marrow, indicated by a lowered neutrophil count, while the less penetrating radiations may appear first to affect the lymphocytes (which, however, are as remarkable for their recuperative powers as for their sensitivity).

Goodfellow's (1935, 1936) classical papers amplify Mottram's and likewise draw attention (by way of contrast with the effects of radium) to the blood picture of healthy controls none of whom had come into contact with any form of radio-active agent (Table 1). Over eight consecutive days the total white counts for the whole series varied between 4,700 and 8,700 cells, and the lowest count of all (4,700 cells on the third day of counting) showed by the seventh day of counting a total of 8,100 white cells; variations of a similar order occurred throughout this "control" group, and Mottram's figures for "normal" variations are much the same. Goodfellow pointed out that the cardinal feature of this "normal" variation was its essential lack of order or conformation to a recognizable rule or rhythm, in contrast with the "orderly and progressive changes" of a pathological tendency due to radiation. He found that the changes in the circulating blood of patients undergoing radium treatment were so constant and definite that it was possible to relate in graphical form a given quantity of therapeutic irradiation to the daily percentage lymphocyte fall (Fig. 2)—a finding which he suggested would be valuable in estimating permissible doses of irradiation to patients, and which could also be applied to save a certain amount of hæmatological investigation in patients undergoing massive dose radium treatments.

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TABLE I.—TO ILLUSTRATE NORMAL VARIATION OF BLOOD COUNTS (NO EXPOSURE TO RADIATION)

(Goodfellow, D. R., 1936, <i>Acta radiol.</i> , Stockh., 17, 29)							
Case No.	Days	Total W.B.C.	Neutrophils	Lymphocytes	Mono-cytes	Eosino-phils	Baso-phils
C. 1.	0	5,200	3,037	1,269	811	73	10
	1	5,500	3,378	1,308	748	55	11
	2	5,100	2,887	1,418	724	61	10
	→3	4,700	2,370	1,504	714	84	28
	4	6,600	4,053	1,570	885	79	13
	5	6,000	3,096	1,596	1,176	84	48
	→7	8,100	5,379	1,733	859	129	—
	8	6,000	3,450	1,770	660	120	—
C. 2.	0	5,400	2,700	1,480	1,069	108	43
	1	7,400	4,661	1,614	918	133	74
	2	7,700	4,620	1,709	1,140	154	77
	3	7,800	4,368	1,825	1,342	187	78
	4	6,000	3,600	1,500	768	84	48
	5	6,200	3,447	1,587	980	99	87
	7	6,700	4,020	1,849	697	121	13
	9	5,800	3,259	1,670	650	127	94
C. 3.	0	6,000	3,892	2,304	708	84	12
	1	5,700	2,986	2,086	468	137	23
	2	5,400	2,602	2,257	422	98	21
	3	6,700	3,350	2,572	563	134	81
	4	6,400	3,553	2,266	512	76	13
	6	8,400	5,998	1,598	621	50	33
	8	5,300	3,010	1,548	488	212	42
C. 4.	0	7,500	4,440	1,950	855	165	90
	→1	8,700	4,611	2,627	1,009	313	140
	2	7,400	4,558	1,791	918	118	15
	3	7,400	4,499	1,865	784	222	30
	4	7,700	5,298	1,540	662	123	77
	6	5,400	3,452	1,198	573	65	22
	8	6,000	4,032	1,200	624	96	48
C. 5.	0	5,700	3,260	1,688	502	171	79
	1	5,500	3,188	1,682	495	154	81
	2	5,800	3,480	1,740	476	81	23
	3	5,200	2,663	1,692	562	166	114
	4	6,900	4,306	1,877	565	138	14
	6	6,000	3,600	1,716	552	60	72
	8	6,100	3,600	1,842	524	122	12
C. 6.	0	7,300	5,036	1,431	730	73	30
	1	7,900	4,250	2,227	1,216	142	65
	2	5,000	2,940	1,360	600	80	20
	3	5,300	3,218	1,325	620	106	31
	4	6,300	3,642	1,840	668	138	12
	5	7,400	4,336	2,116	740	192	16
	7	7,000	4,340	1,610	938	84	28
	8	6,600	3,603	2,032	872	80	13

Increase in circulating *immature* leucocytes is a finding which can have value as a signal of radiation damage, and though admittedly tedious as a routine, the graphical demonstration of a "shift to the left" of the neutrophils, as illustrated by Fig. 4 (Nordensen, 1946) may on occasion be something more than an interesting exercise in hæmatology.

It is convenient when selecting candidates for training as technicians in X-ray or radium work, to fix minimum standards for the blood picture. That of the International X-ray and Radium Protection Committee (1933) was accepted for many years as a minimum total of 6,000 white cells per c.mm. of which 1,200 must be lymphocytes. This was subsequently altered in the light of increasing experience (and kilovoltages) to 5,000 leucocytes and 1,500 lymphocytes per c.mm (1948) by the British X-ray and Radium Protection Committee. Turner (1953), commenting on "the tacit assumption that below these limits the state of the blood is unsatisfactory and that any further depression of a 'leucopenia' would seriously reduce resistance to infection" compares the sickness absence of a group of workers at A.E.R.E., Harwell, who had a leucocyte range 3,700 to 7,700 per c.mm. with a control group whose counts were in the accepted normal range of 4,500 to 13,300. The "leucopenic" group showed not only a less incidence of disease, but if they did become ill, showed a tendency for

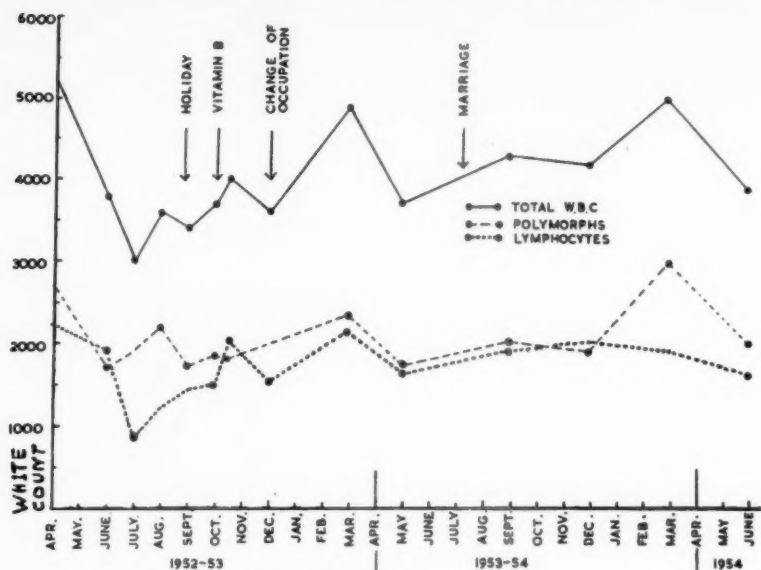
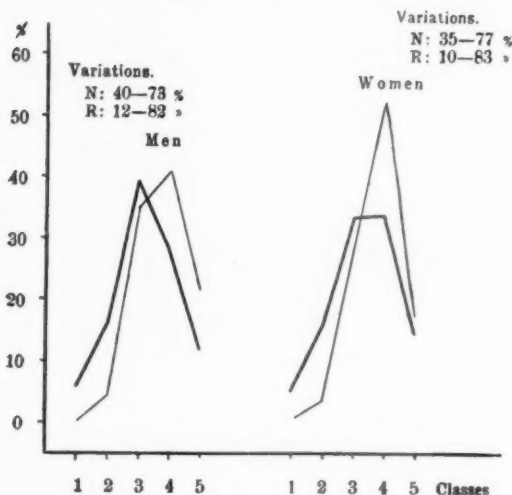


FIG. 3.—Rhythmical variation in white count over three years.

FIG. 4.—Neutrophil "shift" as index of premature leucocytes in circulating blood. (Nordensen, N. G., 1946, *Acta radiol., Stockh.*, 27, 425.)

the clinical course of their illness to be shorter than did the control ("normal") group. Turner concludes that selection for employment in a radiation hazard should be the clinical assessment of general health in conjunction with the blood count, and that rejection should not invariably follow repeated total white cell and lymphocyte counts below values hitherto considered to be the lower limits of normal.

A radiotherapist speaking on radiation hazards cannot hope to escape the question of genetic effects produced by X and gamma rays on germinal cells. Catchside (1947) has given a very useful account of the experimental evidence for our purposes; it includes, of course, the basic fact that the chances of a spontaneous mutation occurring per generation in any particular gene is of the order of one in 10^6

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Stern (1947) the figure while according to 0.1 per cent the rate of this maximum over the normal.

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He remarks giving reformation either gametization is an effective fortunate and (when radiotherapy between).

Before Mr. Anscombe Here is to nursing.

or 10^6 and this rate is doubled by a dose of 50 r. He goes on to remark that the proportion of mutation rate to dose in a variety of organisms is remarkably constant, tending to suggest that it might be of much the same order for yet other organisms, including man; and since gene mutations follow intense local ionization at or very close to a gene (or are produced by a direct hit, if anyone wishes to insist on the target theory), the mutation rate will be lower in a mammal than in *Drosophila* only if the gene happens to be smaller, which is unlikely. On this basis it has been calculated that a man receiving a dose of the order of 2 r every month for two years, would double his mutation rate, in other words further changes would probably be for the worse. On the other hand, it seems unlikely that an increase in deleterious gene mutations will be noted in the immediate future, even if allowance is made for increasing use of X-rays for diagnostic purposes over the last fifty years; it has been suggested that twenty to forty generations will need to elapse before an increase of hereditary abnormalities due to this cause is likely to be observed at the present rate of radiation.

Stern (1949) who also gives an excellent account of radiation genetics, chooses "arbitrarily for man, the figure 200 r as the dose which induces the same number of gene mutations as occur spontaneously", while accepting 50 r as the figure for *Drosophila*. He estimates that a worker receiving a dose of 0.1 r per working day would accumulate over ten years an amount of radiation capable of raising the rate of gene mutations by 150%, but that if the average daily dose were restricted to one-tenth of this maximum, the worker would receive less than 30 r over ten years, equivalent to a rise of 15% over the natural gene mutation rate.

I can here do no more than mention Dobzhansky (1951), Lea (1946), and Müller (1927) whose discovery of the mutagenic effect of X-rays did so much to promote modern genetic research, but Spear (1953) warns against failure to differentiate between effects of radiations as a cause of gene mutations, and on the other hand of structural changes in chromosomes. A gene mutation may not become apparent for many generations, and indeed, if recessive, will not appear even though heritable, unless a gene with which it is paired has undergone a similar mutation. Changes in the structure of chromosomes, however, which cause mechanical difficulties at division while permitting survival of the cell (instead of causing death as more frequently happens) will produce heritable changes (in the offspring) analogous to gene mutations but often of a dominant character. Such "chromosome abnormalities" may cause damage or infertility in the first generation offspring, and in this respect are far more detrimental than induced gene mutations (which are usually recessive in character).

He reminds us further that the effects of irradiation on the zygote, shortly after fertilization, while giving results similar to those following the exposure of ova in general (retarded development or formation of abnormalities) are far more damaging than those which follow comparable exposure of either gamete; and again of what must invariably inform any treatment plan for "radiotherapeutic sterilization" in the female, namely that "after the first month (of pregnancy) the most likely injury is an effect on the central nervous system, where mitosis is particularly active at this time". Unfortunately this effect on the central nervous system is not always incompatible with life of the foetus, and (when it has survived) I have met cases so tragic that I offer no apology for reminding my fellow radiotherapists of this hazard. The remedy is, of course, to ensure against any possibility of conception between the time of the diagnostic curettage, and the application of radiation to the pelvis.

Before discussing the following measurements, I wish to thank our Principal Hospital Physicist, Mr. Anson Quinton, and his staff, particularly Mr. H. Besford.

Here is a very simple investigation, carried out some years ago now in an attempt to demonstrate to nursing staff the undesirable effects of "bunching" together patients undergoing radium treatment.

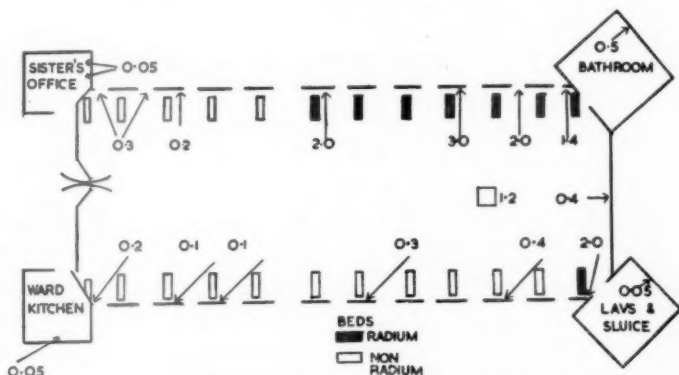


FIG. 5.—"Radium beds" in a gynæcological ward.

A typical "Florence Nightingale" ward in a general hospital is shown with beds set aside for "gynaecological radium", and test films have been exposed at points on the walls, during the whole period when treatment was going on (about five days with a quantity of radium of the order of 50 or 70 mg. to each patient) (Fig. 5). The distribution of the radium risk is, as would be expected, highest in the centre beds of this "radium corner", and since the films are on the walls, it is permissible to multiply by a factor of at least 12 to estimate the dose-rate at the bedside (on a level, say with the patient's pelvis). In certain circumstances quite a serious hazard might be created. The experiment also illustrates the value of distance as a protection factor and also walls of good brick.

In connexion with the nursing problems, experience teaches the radiotherapist, to beware, as elsewhere, of the argument of "convenience", and the blandishments of Ward Sister or protests by Matron must be received with caution. Fig. 6 is a "block" graph to illustrate nursing conditions in an eight-

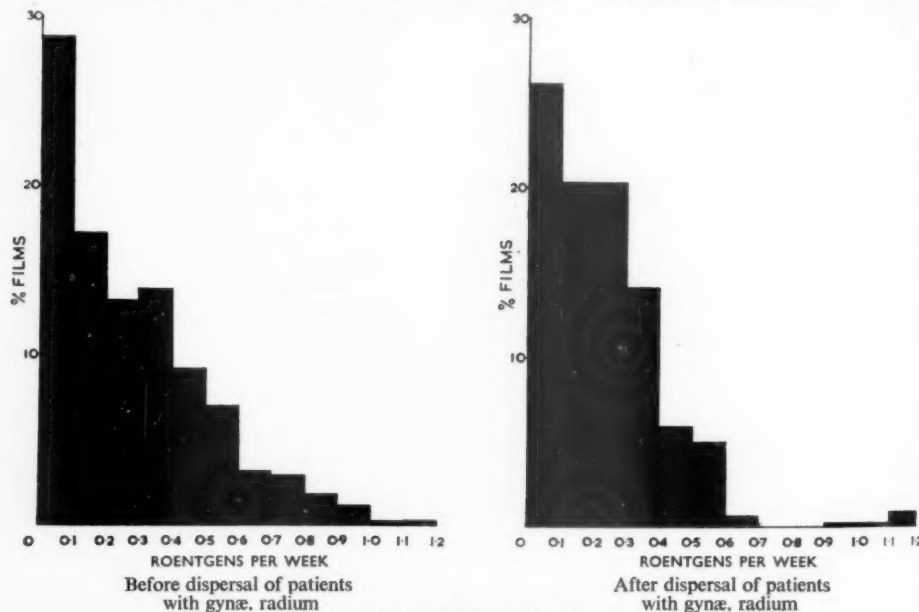


FIG. 6.—Radium ward nurses.

bed ward (about 450 sq. ft. floor area) in which female radium patients were accommodated together "for convenience of nursing"—it was urged that there would be less danger of losing radium, and that nurses would not need to pass the beds on their way to other patients. The "blocks" show percentages of test films lying in the dose ranges 0-100, 100-200 &c. up to 1,200 mr per week, and in the above conditions the average dose per nurse was 333 mr, while 17.3% of test films recorded doses of 500 mr or over. The patients were next dispersed through a larger ward so that no two were side by side and the result is illustrated by a significant shift to the left of the "blocks"; the average dose per nurse per week is reduced to 280 mr and only 7% of nurses now record more than 500 mr per week.

A graph of the average dose per nurse per week against amount of radium in use in the eight-bed ward (before "dispersal" of patients) shows that up to a total of 200 mg. the relationship is approximately linear. Beyond this the curve deviates from the linear relationship in the direction of increasing dose measured. With a certain minimum number of patients, a nurse will receive a radiation dose mainly (indeed almost solely) from a particular patient whom she is attending, and what may be called the "background contribution" from other patients undergoing radium treatment is negligible. When this minimum is exceeded the "background contribution" from other patients becomes increasingly significant, and this is illustrated by the deviation of the graph from a straight line. The quantity of 200 mg. radium in use corresponds in a room of this size to 4 patients. After "dispersal" the "background contribution" is reduced and the graph becomes more linear (Fig. 7).

We have been at pains to break down the dose recorded by radium ward nurses (a fairly consistent average at one time of the order of 300 mr per week with a maximum up to 600 mr) into some of its components, and have now little doubt of there being two main causes of high mr doses: first, backs; in a nursing training school there is a great tradition of "doing backs" frequently, to avoid the disgrace

of bed-sores, and a "back round" three times a day is not at all uncommon at our hospitals. If a particular "back" happens to be in close proximity to 60 or more mg. of radium, the nurse's mr dose will be proportional. The other fruitful source of high dosage is the evening and night immediately after the "operation list", when patients experience post-anæsthetic distress of various kinds such as cyanosis, restlessness and vomiting. Apparently it is a tradition that the nurse must hold the patient's hand at these trying times, and certainly it does seem that she is inclined to expose herself unnecessarily to radium dosage. Speed and expeditiousness in any duties near to patients are lessons of nursing on a radium unit, and it is, of course, essential that the number of nurses must invariably be "up to establishment" (with particular reference to the evenings of operating sessions)—a point of view which does not always commend itself to hospital Matrons.

Repeated handling of mass quantities of radium (e.g. for moulds and intracavitary applicators), by one or two members only, is a continual problem for radiotherapy staff, and my own department

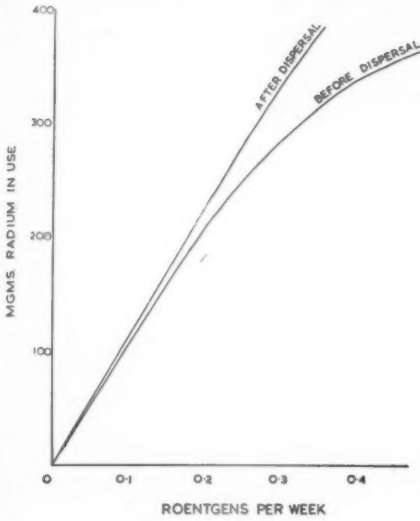


FIG. 7.—Ward nurses.

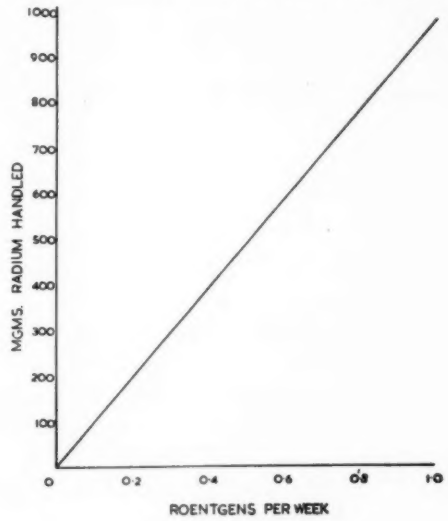
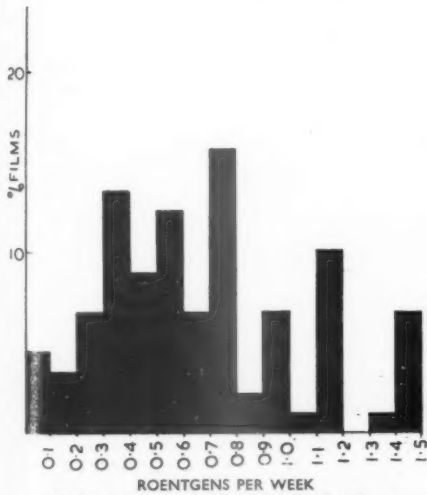
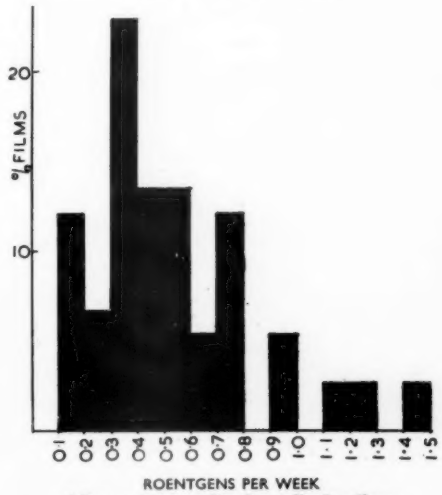


FIG. 9.—Radium nurses.



Before permanent "make-up" of radium



After permanent "make-up" of radium

FIG. 8.—Radium duty nurses.

has tried to distribute this risk by employing two "Radium Duty Nurses" (who do no other duty in radium wards and are changed every three months), to take over certain processes which involve breaking down and re-making up radium. "Block" graphs illustrate the percentages of their test films lying in the dose limits 0-100, 100-200 &c. up to a limit of 1,500 mr per week. The average dose per week per "Radium Duty Nurse" was estimated to be 710 mr per week (with a maximum of 1,500 mr), and 63.3% of test films recorded doses of 500 mr or over (Fig. 8). To reduce this, a number of applicators were made up in permanent form which eliminated dismantling of individual radium containers for cleaning and inspection. The result is illustrated by a shift to the left in the "block" graph; the average dose per "Radium Duty Nurse" per week is reduced to 560 mr, and the percentage of test films recording 500 mr or over, becomes 45%. The graph of average dose recorded by "Radium Duty Nurses" against the amount of radium handled, refers to the former period (before permanently made up applicators) and turns out as one might expect, to be linear (the "amount of radium handled" figure is a compromise between radium being made up and radium broken down for remounting and cleaning) (Fig. 9).

Fig. 10 is an investigation of a one-roomed diagnostic X-ray department, performing some 400 examinations a week of miscellaneous cases. At first sight one might possibly question the safety of technical staff (some preliminary dental film tests had caused uneasiness) but a full investigation revealed that PROVIDED ACCEPTED SAFETY PRECAUTIONS WERE OBSERVED no worker need be exposed

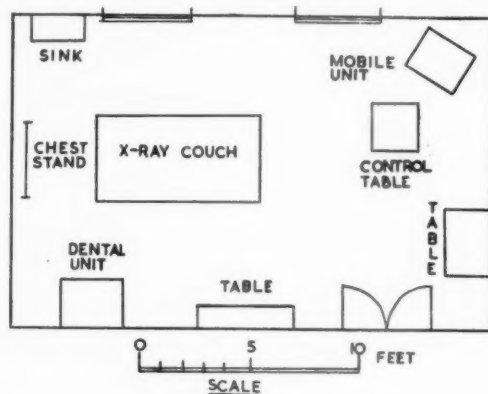


FIG. 10.

to a dose exceeding 100 mr per week—a safety factor of five. The room has a floor space of 300 sq. ft. (i.e. accords with International Recommendations) and readings taken by means of a Phillips monitor (incorporating a Geiger-Müller counter) and a Victoreen dosimeter fitted with a specially large ionization chamber, at positions occupied by the radiographer during her day's work, all give satisfactory readings as shown in Table II.

Nature of examination	kV.	mA-secs.	Cone diam.	F.S.D.	Dose-rate close to control unit	Dose
Spine	68	160	8"	40"	80 mr/hr.	0.18 mr
"	72	230	"	"	120 "	0.39 "
"	68	200	4"	36"	80 "	0.24 "
"	79	600	8"	"	130 "	1.2 "
"	79	600	"	"	110 "	1.0 "
Chest	70	10	"	72"	50 "	0.001 "
"	77	15	"	"	50 "	0.002 "
Arm	50	25	"	36"	12 "	0.004 "
"	41	20	4"	40"	10 "	0.003 "
Leg	65	30	"	36"	60 "	0.02 "

The highest dose of 1.2 mr and the next highest of 1.0 mr are accounted for by lateral views of the spine (one in a "rather thick" patient), while for the examination of the leg the radiographer stood a little nearer than usual to the end of the couch.

Danger, of course, might arise if the work in this one room were to increase so as the lead to undue rush and hurry and ultimately to neglect of the "safety-drill" (e.g. discarding the radiographic cone), but this is inevitable in any protection system and cannot be advanced as fair criticism of existing conditions.

Diagnostic radiologists are all familiar with the special hazards of fluoroscopy. Barclay in collabora-

tion with Sydney Cox (1928) suggested that a "harmless" exposure figure for diagnostic radiologists would be of the order of 0.008 U.S.D. in thirty days. If it is permissible to estimate the value of the then U.S.D. in terms of roentgens at 500 r or less, the figure is equivalent to a dose of rather less than 0.7 r per six-day week—one of those brilliant approximations (or ought one to say "prophecies") which all who knew him will recognize as so characteristic.

Archer *et al.* (1952) use spun lead glass as protective material, made up into coats, aprons and curtains; one thickness is equivalent to 0.035 mm. of lead, and no heavier in appropriate "plies", than the conventional lead rubber apron of the same protective value.

Though Grimmer and Read's (1936) account of a method of dealing with the mass of radium in a beam unit is now only of historical interest, it remains an example to radiotherapists and physicists alike, for its description of meticulous and painstaking physical investigation of every single room in a large building. They describe how 5 grams of radium were conveyed "on a long handle" by nurses from a safe to the radium beam unit after the radiotherapist had set the empty beam-head in position. The time required for the transfer varied from 10 to 20 seconds, and on an average a nurse might perform this duty "not more than twelve times a day"; yet the highest total dose (measured by Sievert chambers) for one week was 0.55 r, the lowest 0.1 r and four others less than 0.3 r, a striking example of what intelligent co-operation and drill can accomplish.

In connexion with risk in operating theatre work involving radium, Table III, based on the paper by Miller and Walter (1950), is interesting to radiotherapists.

TABLE III		
Radium "risk" per average case expressed as mg.-hours	Gynaecological (intra-cavitary)	Interstitial (implant)
	3.75	4.5
Dose recorded on fingers	490 mr	180 mr
" " face	16 "	20 "
" " trunk	14 "	16 "
" " legs	8 "	8 "

For gynaecological work the amount of radium risk (expressed as mg.-hours) is smaller than for the average implant, although the gynaecologist tends to use larger average quantities of radium. Presumably "insertions" can be performed more rapidly than an implant. However, gynaecology imposes two and a half times as great a dose on the fingers. During an implant the dose on the face is larger than during a gynaecological "insertion" (it appears that the implant demands more stooping over the site of operation); while the dose at feet level is the same for both. It may be that once the larger quantity of intracavitary radium is in situ, the bulk of the pelvis acts as a better screen than do tissues of the usual implant sites.

The above doses, of course, are average values, and there are considerable variations for different operators and different types of case. For both (implant and intracavitary) the average dose on the abdomen over a whole operating session is usually less than 150 mr.

Dose recorded by theatre staff in one week (2 theatre sessions)

Theatre Sister	..	150 mr
Theatre Nurse	..	120 mr
Theatre Orderly	..	60 mr

Wilson (1945) gives a useful rule for rapid estimation of "safe" distances from any given quantity of radium. The original calculation was based on the then accepted tolerance dose of 10^{-6} r/sec. but Dr. Wilson, in a personal communication, has indicated that the lately accepted tolerance intensity of 4×10^{-6} r/sec. exists at a distance of 1 metre from a 17.2 mg. mass of radium screened by 0.5 mm. platinum (on the basis that 1 mg.-element-hour at 1.0 cm. equals 8.4 r). The corresponding "safe" distance from any other given mass of radium can then be calculated by means of the inverse square law, from the formula

$$d \text{ (in cm.)} = 24.2 \sqrt{m \text{ (in mg.)}}$$

This has sometimes proved useful in making estimations at a bedside (e.g. to decide whether or not a particular bed need be moved), or in connexion with temporary disposition of radio-active material in any quantity.

Nuttall (1939) has summarized very adequately the usual means by which radium workers sustain harmful effects, namely by ingestion, inhalation, handling and long-term exposure, with (at that time) appropriate emphasis on handling and general irradiation over long periods. Experiences with the New Jersey luminous dial painters (Martland, 1929) focused attention on the ingestion hazard and its sequelae including development of bone sarcoma (Martland and Humphries, 1929; and Martland, 1931), but it was subsequently thought that this particular risk is unlikely to arise in clinical practice. The advent of radio-isotopes has again brought into prominence these two hazards (inhalation and ingestion), so that it is pertinent to remark that the number of "research projects" which involve use of isotopes is an index of the need for renewed caution and closer supervision of technical workers. Two outstanding points demand special attention: first, the effect of alpha and beta particles from a source (however small) anywhere in the body cannot be ignored, since though their range is short

(that of the alpha particle is less than 1.0 mm.) yet within that range they have potentialities for ionizing several hundred times as densely as gamma rays; and second, that the half-life of some isotopes (e.g. strontium) is extremely protracted, and this is a serious matter when ingestion is in question, or if their administration to living patients is being considered. On the other hand, the large-scale use of very short-lived isotopes does not invariably appeal to the luckless individual to whom falls the task of handling and conveying the ever-increasing weights of lead containers (Mayneord, 1951); indeed the alternative (and not unlikely) possibility is that the same individual will ultimately solve this problem by dispensing with the greater part of the weight (and along with it most of the protection) while relying on increasing fleetness of foot to cut down his exposure.

The British X-ray and Radium Protection Committee, under the chairmanship of the late Sir Humphry Rolleston, produced in July and December 1921 the first memoranda on the subject, which later were accepted by all countries at the Second International Congress of Radiology in Stockholm (1928) as the basis of the International Committee's Recommendations. Their foresight and energy laid the foundations of the protection which is the safeguard of our work to-day. Names of that first Committee were:

Sir Humphry Rolleston	(St. George's Hospital and Cambridge University)
Chairman.	
Dr. Stanley Melville ..	(The Brompton Hospital and St. George's Hospital)
Professor Sidney Russ	(Middlesex Hospital Medical School)
	Hon. Secretaries.
Sir Archibald Reid ..	(St. Thomas's Hospital)
Dr. Robert Knox ..	(The Royal Cancer Hospital)
Dr. Harrison Orton ..	(St. Mary's Hospital)
Dr. Gilbert Scott ..	(The London Hospital)
Dr. J. C. Mottram ..	(The London Radium Institute)
Dr. G. W. C. Kaye ..	(National Physical Laboratory)
Mr. Cuthbert Andrews	(The Roentgen Society)

Out of a Committee of 10 members 7 were medical men, and we, as radiologists, should continue to take an active part in everything appertaining to radiation hazards and their elimination. Professor Mayneord in his Silvanus Thompson Lecture for 1951 remarked that "measurements can now easily be made, but their significance is very difficult to determine and it would be a great advantage if clinical records of all persons coming into the service could be kept in considerable detail", and "the physical and clinical investigation must go hand in hand".

Here then is a clear challenge to radiologists, both diagnostic and therapeutic: to make their contribution towards the advancement of the protection and safety of all who work with this "intolerable radiancy".

I cannot do better than borrow from my old favourite, Leonardo da Vinci, a quotation so appropriate that it springs at once to mind. It is this: "Truly it so happens, that where reason is not, its place is taken by clamour. This never occurs when things are certain. Therefore where there are quarrels, there true science is not; because truth can only end one way—wherever it is known, controversy is silenced for ever."

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Section of Surgery

President—HAROLD C. EDWARDS, C.B.E., M.S., F.R.C.S.

[October 13, 1954]

Observations on Splenectomy in Disorders of the Blood

PRESIDENT'S ADDRESS

By HAROLD C. EDWARDS

THE observations I am about to make are based on a study of 71 patients for whom splenectomy has been done for various abnormal conditions or behaviour of the circulating blood, and I have to thank my surgical colleagues at King's College Hospital, where nearly all the operations were performed, for allowing me to include patients operated upon by them. I am particularly indebted to the past and present haematologists at the Hospital—the late Dr. E. ff. Creed, Dr. J. V. Dacie, now at Hammersmith, and my present colleague, Dr. William M. Davidson, and to my physician colleagues.

When a surgeon is asked for an opinion as to whether splenectomy is indicated in the case of Mrs. A in the Medical Ward, the records of whose investigations already cover several quarto pages, he knows quite well that her fate has already been decided more or less by her physician and the haematologist. He still has a part to play, however, as it is for him to decide whether splenectomy is advisable, from his standpoint, in her case. On two occasions, for example, operation was urged on the grounds that the spleen was causing great distress because of its size, the patient being to all intents and purposes bedridden. Even if the prognosis were hopeless, and the blood dyscrasia uninfluenced by splenectomy, it was pointed out that the patient would be benefited, and spend his remaining days in greater comfort. One was a woman of 75 suffering from lymphatic leukaemia, who survived four years; one was a man of 46 suffering from myelosclerosis (of whom more later) who lived a useful life for another two years and five months.

Pain may influence action. Exploration upon a boy of 12 with aplastic anaemia, from which disease his elder brother had died, was undertaken because of recurrent attacks of violent upper abdominal pain, thought at one time to be due possibly to recurrent intussusception. Nothing abnormal was found other than a rather large spleen, which could not be felt clinically. Dr. Dacie was in the operating theatre at the time, and we thought we might take the spleen out. Not only was the pain cured, but also, *mirabile dictu*, the anaemia. The pallid boy of 12 was a lusty man of 27 when last I heard, married, and with a healthy offspring, his only blood abnormality being a relative lymphocytosis (W.B.C. 10,000; polys. 46%; lymphos. 49%).

A woman of 39, known to be suffering from pulmonary sarcoidosis, complained of constant pain over a moderately enlarged spleen, which had been exposed to deep X-rays. Removal of the spleen not only cured this symptom, but led to considerable improvement in general health. To-day, five years later, though the sarcoidosis of the lungs has increased, there is no anaemia.

The risk of splenectomy should naturally be considered. It has been reduced a lot during the past ten to fifteen years. Of 24 patients operated on before 1940, 4 died. One was a fulminating purpura who bled to death; one, also a purpura, died from peritonitis; one, an aplastic anaemia, aged 64, and the fourth a very severe acholuric jaundice aged 48, died from pneumonia. Of 47 patients operated on since that date, 2 died. Both were a "last resort" type of case. One a stout woman of 64 suffering from myelosclerosis died from a pulmonary embolism on the third post-operative day; and the other, a woman of 59, who was suffering from severe haemolysis associated with Hodgkin's disease, died one week after operation.

Does splenectomy influence longevity? Of 65 patients who survived the operation, 18 are now known to be dead. 9 of these died within a few months or years after operation, and were cases for which splenectomy was performed as palliative, but without hope of cure.

The primary diseases were: Banti 3, Hodgkin 3, atypical leukaemia 1, lymphatic leukaemia 1, myelosclerosis 1.

9 who died had suffered from haemolytic anaemia of the chronic type. 4 were atypical and at least 2 of these died from recurrence of haemolysis. One died from uraemia twenty years after a successful result, and another from hyperpiesis, known to have been present before operation.

The other 5 were all typical familial acholurics who were cured of all symptoms, but died young. 3 of them died from cerebral haemorrhage—the ages being 29, 29, and 44; and one from a virulent pneumococcal septicaemia at 33 years. At post-mortem, haemorrhages were found in both adrenals.

JAN.

To avoid relegating himself to the role of general clinician and craftsman, however, the surgeon should make some attempt to understand the reason *why* splenectomy so often does so much good in the well-selected case. The problem of selection is, of course, another matter.

The term "hypersplenism" implies that the spleen is exerting its normal powers too drastically—and not, necessarily, that it has taken on malicious powers, although this may be possible. It is not strictly parallel with hyperthyroidism.

The normal powers of the spleen are: (a) The elimination of effete cells from the blood. (b) Inhibitory control of hæmopoietic activity either by delaying of maturation, or by impeding release of cells into the circulation. (c) The production during foetal life of all three formed elements of the blood, a function which may be restored if the bone-marrow is invalidated by sclerosis or fibrosis, or by secondary malignant disease.

Whether the spleen is capable under certain circumstances of producing a toxic, or an immunological effect, or can influence the permeability of the capillary walls, is still conjectural.

The term "secondary hypersplenism" is impossible to define with accuracy, because it is doubtful if there is such a thing as *primary* hypersplenism, i.e. a condition in which the only factor is heightened splenic activity. Nevertheless, secondary hypersplenism is a useful clinical term. It refers to the development of increased splenic activity in one particular or another during the course—often in the later stages—of another disease in which splenomegaly is a feature, such as what we used to call Banti's disease; Gaucher's disease; lymphatic leukaemia; Hodgkin's disease; &c. The result of hypersplenism may be an acute or chronic hæmolytic process, or purpura. In the more chronic diseases the effect of hypersplenism may conceal the true nature of the malady.

Splenectomy in certain cases of this type (Banti's probably excluded) may be well worth doing, for although it does not necessarily increase longevity, it may materially improve vitality, and allow the patient to live more effectively his remaining months or years.

In all conditions in which hypersplenism exists, splenectomy is most likely to be effective if the bone-marrow shows active hæmopoiesis, or contains in liberal quantities the precursor of the element or elements in which there is a deficiency in the circulation, although our experience is that this healthy appearance of the bone-marrow is not necessarily a *sine qua non* of success.

There is a direct relation between the size of the spleen and the severity of the effects of hypersplenism. Hence the bigger the spleen, the better the result.

Table I is a classification of the various conditions for which splenectomy was performed, together with the results obtained.

TABLE I.—CONDITIONS FOR WHICH SPLENECTOMY WAS PERFORMED

	No.	Op. deaths	Good	Response Partial	None
(1) <i>Hæmolytic anemia</i>					
(a) Familial typical	24	1	23	—	—
(a) Familial atypical	3	—	2	—	1
(b) Acquired typical	3	—	3	—	—
(b) Acquired atypical	3	—	2	1	—
(c) Unclassified	3	—	2	1	—
(d) Acute acquired	1	—	1	—	—
(e) Associated with:					
i. Atypical leukaemia	1	—	—	—	1
ii. Hodgkin's disease	1	—	—	—	1
iii. Porphyria congenita	1	—	—	—	1
iv. Lymphatic leukaemia	1	—	—	—	1
(2) <i>Leukemia</i>					
(a) Primary neutropenia (?)	1	—	—	1	—
(b) Felty's syndrome	1	—	1	—	—
(3) <i>Thrombocytopenic purpura</i>					
(a) Essential	10	2	5	1	2
(b) Secondary to Hodgkin's disease	1	—	1	—	—
(4) <i>Pancytopenia</i>					
(a) Primary hypersplenism (?)	1	—	1	—	—
(b) Aplastic anemia	4	1	2	—	1
(c) Secondary to:					
i. Myelosclerosis	3	1	2	—	—
ii. Aleukaemic leukaemia	1	1	—	—	—
iii. Banti's disease*	5	—	—	—	—
(5) <i>Miscellaneous</i>					
	<i>Reason for operation</i>				
(a) Hodgkin's disease	1	—	1	—	—
(b) Sarcoidosis	1	—	1	—	—
(c) Lymphatic leukaemia	1	—	1	—	—

*3 died within five years, 2 from hæmatemesis. 1 untraced after two years. 1 recent case cured of hypersplenism.

(1) HÆMOLYTIC ANÆMIA

27 of these 36 patients suffered from familial hæmolytic anæmia or acholuric jaundice.

Sometimes, however, one meets a patient with an undoubted family history, a large spleen, but with no spherocytes and no increase in fragility. This has happened 3 times in our experience, the best example being the one marked + in the family tree (Fig. 1).

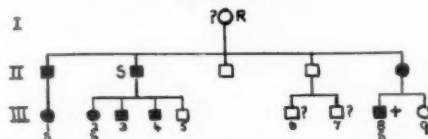


FIG. 1.—Genealogical tree. Familial hæmolytic anæmia: square symbols, males; circular symbols, females; black: spleen palpable; white: no evidence of splenomegaly; R, refused to be examined; S, splenectomy; + no increased fragility, no spherocytes.

There are 6 examples of anæmia typical of the familial type, but with no "family history", and 3 patients who could not be classified with certainty.

Splenectomy is strongly indicated in the familial type, with a characteristic blood picture. It is, in fact, uniformly successful. The most dramatic results were obtained in the very young, who suffered acute hæmolytic crisis; but older people may also benefit by an increase in all-round health after splenectomy.

The 3 relative failures of splenectomy in this series were all in-patients with atypical hæmatological findings.

A family history is often of the greatest importance in diagnosis, particularly in infants, for in them the blood and bone-marrow may show misleading features during a crisis. There may, for example, be a reticulopenia and a hypoplastic marrow. In one instance, that of a little girl of 9 months, the test for fragility was made meaningless, for the child had been kept alive by repeated transfusions since the age of 6 months. Dr. Wilfrid Sheldon, under whose care the patient had been sent, was, in fact, inclined to a diagnosis of Cooley's anæmia (which is not likely to be benefited by splenectomy) until the child's mother was found, herself, to have increased fragility. Splenectomy produced the most dramatic result we had ever seen in acholuric jaundice. No further transfusions were needed, and the child was converted in a week or two into a normal healthy child. Later we learned that Mr. W. McMurray of Newcastle had removed the mother's spleen when she was 8 years old.

Gall-stones formed in 8 of these patients, the youngest being 20. Usually they are tiny "multiple" stones, and may be radio-opaque as illustrated in Fig. 2. The patient, a woman of 60, had complained



FIG. 2.—Radio-opaque gall-stones associated with hæmolytic anæmia.



FIG. 3.—Cholecystogram displaying large gall-stones in a man of 35 suffering from atypical familial hæmolytic anæmia. Calcified mesenteric glands are also present.

of biliary colic and was found to be suffering from an atypical acquired form of hæmolytic anæmia (Dr. Samuel Oram's patient). The stones may, however, be larger as illustrated in Fig. 3. The patient is a man of 35, with a familial link in his history, but without increased erythrocyte fragility (Dr. Terence East's patient).

In both these patients the gall-bladder was removed at the time of operation, because its wall was thickened. We do not think it is necessary to remove the gall-bladder if the wall seems normal, but sufficient to open it and wash it out with saline, using a Higginson syringe, and then closing it without drainage.

A little time ago I operated on a man of 48 because he had what seemed to be gall-stone colic two years after splenectomy. I found no stones, and confirmed by cholangiography that the common bile duct was clear (Fig. 4). I did not interfere, but I feel now that perhaps I ought to have removed



FIG. 4.—Operation cholangiography upon a man who complained of biliary colic two years after splenectomy for familial acholuric jaundice. No cause for the colic could be found.



FIG. 5.—A spleen of about normal size and shape which was found fifteen years after splenectomy performed for familial hæmolytic anæmia upon a woman then aged 47. The operation was undertaken to remove a gall-stone from the gall-bladder, which is seen retracted to the left. The liver lies above, the new spleen being situated at the porta hepatis.

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FIG. 6.—A spleen of about normal size and shape for forty years after splenectomy for malignant disease.

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the gall-bladder. Time will tell. Incidentally, my colleague Mr. A. J. Heriot performed a splenectomy on a patient of 60 who had had a cholecystectomy at 40. The common bile duct appeared to be quite normal.

The object of the operation for hæmolytic anæmia is to remove all splenic tissue, for it is on record that splenunculae left behind may grow within a few years to the size of the removed spleen, with recurrence of the disease. But even if all the "anatomical" spleens and splenunculae are removed, the reticuloendothelial system can grow more splenic tissue, as the following case illustrates.

A woman of 62 was successfully treated for typical familial hæmolytic anæmia by splenectomy fifteen years ago. Recently she had suffered attacks of biliary colic, and cholecystography had demonstrated the presence of a gall-stone. In the course of removing this stone, I found a medallion of splenic tissue limpeted on to the undersurface of the liver (Fig. 5). The patient is clinically well, and there is no evidence at present of hæmolysis (Hb 88% (Haldane); reticulocytes 0.4%).

Chronic intractable ulceration of one or both legs is a feature of the disease in its severest form, and it is claimed that the ulceration readily heals after splenectomy. There are 2 examples in this series: A man of 48, whose brother and two children were also operated upon, who did not survive operation; and a woman of 59 who was operated upon by Mr. E. G. Muir (Fig. 6A). The ulcers healed in six weeks, the first time for forty-two years, as they first appeared when she was 17 years old. The patient to-day, eighteen years after splenectomy, and now aged 77, is in excellent general health. She has no anæmia, though the fragility of the red cells is unchanged; a tribute to the operation and a credit to Mr. Muir. But the leg ulcers have returned (Fig. 6B); that on the left leg is malignant, and amputation has now been performed.



A



B

FIG. 6.—A, Patient of 59 with typical familial hæmolytic anæmia. The ulcers on the legs had been present for forty-two years. They healed after splenectomy but recurred in eighteen years. B, The ulcer is now malignant. The patient, now 77, is in excellent general health.

The last 3 patients were referred by Dr. A. Gilpin.

Diagnosis must, of course, be left to one's medical colleagues, but the surgeon must share responsibility when mistakes are made. It is not always easy to distinguish between primary anæmias with splenomegaly, and secondary hypersplenism, for the latter may obscure the real disease, as the following case illustrates. A man of 32 suffered from lassitude for some years. He was found to have a spleen reaching to the umbilicus. R.B.C. 4,000,000; Hb 74% (Haldane); W.B.C. 3,700; platelets 50,000;

fragility normal; bone-marrow—active erythropoiesis. Liver tests were all within normal limits. He was thought to be an acquired hæmolytic anaemia of an atypical pattern. I might add in defence of what I am about to reveal, that the patient was very anxious to have his spleen out, as his uncle had died from a ruptured spleen. The patient had been an in-patient at a psychiatric hospital, and everything considered, I suppose splenectomy was justified.

When I had got the spleen out of the way I noted the liver was nobbly. The pressure in the splenic vein was therefore measured, and was found to be over 400 mm. of water. Later a barium swallow and X-ray showed oesophageal varices. A few months later the blood picture was quite normal: R.B.C. 4,500,000; W.B.C. 10,000; platelets 265,100. He has at least got rid of his hypersplenism, and feels well and happy.

Acute acquired hæmolytic anaemia due to some toxic or immunologic factor is, of course, an entirely different disease clinically, and in this condition one should proceed warily with splenectomy. The following case illustrates this point. A poorly, undernourished, unemployed Jamaican, aged 39, and obviously a very sick man, developed acute hæmolysis following severe pneumonia treated with sulphonamides. The spleen was palpable (Fig. 7A, B). Dr. Clifford Hoyle persisted for four months



FIG. 7.—Acute acquired hæmolytic anaemia following pneumonia treated by chemotherapy.

with conservative treatment, but only temporary improvement resulted. The patient eventually had a hæmolytic crisis of such magnitude that despite transfusion on a very large scale, an adequate Hb level could not be maintained. After many transfusions it once registered 70% but two days later fell to 35%. A spleen weighing 1,200 grams was then removed. Improvement was noted but it was very gradual. Three years later he is fairly well. His Hb is steady at between 70 and 80%, and he is well enough to work. Incidentally, Coombs test for hæmolysins, positive before operation, remains positive.

In this disease, response to splenectomy is, in fact, so variable that cortisone or ACTH either together or separately, is recommended before recourse to operation. As far as I can judge from reading reports, the general feeling is that these hormones are not capable of cure, but may cause so great an improvement as to make splenectomy safer, and a more reliable therapeutic measure.

(2) THROMBOCYTOPENIC PURPURA

The role of the spleen in the aetiology of this condition is more puzzling than it is in acholuric jaundice, and not all of our 10 patients benefited from splenectomy.

The best results were obtained when there was a long history, dating from early childhood, of recurrent hæmorrhages, with very few blood platelets in the circulation, and increased blood platelet precursors (megakaryocytes) in the bone-marrow. In children one should be additionally careful that the diagnosis of thrombocytopenia is fully established before splenectomy is entertained. One

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of our child patients, though clinically well seven years after splenectomy, is not hæmatologically normal, and this is probably due to the overlooking of a splenunculus at operation.

It has been said that if the bleeding time exceeds fifteen minutes, splenectomy is not likely to be of value, but our own experience does not confirm this, for most dramatic responses were observed in patients with bleeding times of 20, 30, and 36 minutes respectively. The last patient is a man of 53, who was operated on at the age of 33. He remains fairly well, and has survived herniotomy and many tooth extractions, although he bleeds a lot. His purpura was preceded by an attack of acute tonsillitis, and it is our experience that if there is an ætiological factor of this nature, splenectomy is not so certain of success.

In a patient for whom an emergency splenectomy was performed after all else had failed, for purpura which followed gold treatment for rheumatism, little impression was made, although she gradually recovered in the end.

Age also is an adverse factor. Our oldest patient developed purpura at the age of 54. After twelve months' medical treatment, splenectomy was done, but was ineffective, and she died from bleeding four months after it. It must be mentioned that in her case, though the platelet count was only 4,000, and bleeding time 15 minutes plus, no healthy megakaryocytes were seen in the bone-marrow—which brings me back to the statement already made, that if the blood disorder is due to a deficiency in one of the circulating elements, splenectomy is most clearly indicated when its precursors are found in liberal quantities in the bone-marrow.

The most serious consequences of purpura is cerebral hæmorrhage, and it is said that this is the usual termination in the patient who does not respond to treatment. One such example was in a woman of 48 who was admitted to the Royal National Hospital under Dr. Macdonald Critchley. She had been unconscious for three days following a spontaneous subarachnoid hæmorrhage. There were no circulating platelets, and sternal puncture showed megakaryocytes but no platelets. The spleen was greatly enlarged. Bleeding time was 30 minutes. Three hours after splenectomy the platelets were 64,000, and the bleeding time 9½ minutes. Ten days afterwards both tests were normal.

She has remained free from purpura for four years, but suffers from mitral stenosis.

One of the difficult problems is how to deal with the fulminating case of thrombocytopenic purpura who does not respond immediately to transfusion with fresh whole blood or possibly platelets in concentration. The reports of treatment by cortisone or ACTH are somewhat contradictory, and no great reliance can be placed on them. None the less, since the advent of these substances, whose action is entirely empirical, there seems to be a trend away from emergency splenectomy. My own feeling is that one should do a splenectomy, this feeling being coloured by knowledge of a recent "medical" death. It is true that one of the cases I have recorded died the day after splenectomy, with blood in the pericardium and pleura. She was desperately ill, with pyrexia, and all the measures then available (this was in 1930) had failed to stay the bleeding.

A year or so ago I performed an emergency splenectomy for secondary purpura associated with Hodgkin's disease, in a man of 22 years (Dr. Terence East's patient). He was bleeding copiously from gums, kidneys, alimentary tract, and subcutaneously. He was losing blood more quickly than it could be replaced. The operation was made difficult because the gentlest handling of the peritoneum and viscera provoked bruising of alarming proportions, but none the less the patient managed to survive. The bleeding stopped at once. Before operation the platelet count was 3,000; fourteen days after operation it was 240,000. The bleeding time had dropped from 10 minutes to 5 minutes, five days after the operation. The bone-marrow contained ample megakaryocytes, suggesting inhibition. The spleen was only moderately enlarged. The patient left hospital well, only to return seven months later to die of the primary disease.

Before leaving this complicated and little understood disorder, I should like to refer to a recent development in research—the discovery of a thrombocytopenic factor in the blood which, when injected into normal people, may produce a prompt fall in platelets, and even bleeding.

(3) LEUCOPENIA (NEUTROPENIA)

Very occasionally the white cells are especially selected for attention, and a leucopenia results. As the polymorphs are mainly affected, the condition is referred to as Neutropenia.

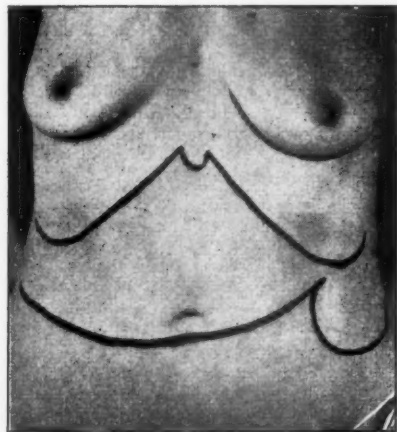
The solitary case in this series of what was thought possibly to be a primary neutropenia was a man of 46, who had a very big spleen. He was referred by Dr. J. L. Livingstone. Operation improved things quite considerably. Before splenectomy the W.B.C. were 1,650, the polymorphs being only 3% and degenerate. After operation the W.B.C. averaged 8,000, and the polymorphs 25%, and were normal. However, he is now deteriorating in health, and to-day, five years after operation, the W.B.C. are a mere 2,700.

He is now under observation ? phthisis.

As for all these conditions, the indication for splenectomy is greatly strengthened if the bone-marrow is hyperplastic in respect of the cells which are deficient in the circulation. This was not the case in this patient, and it is only fair to mention that Dr. W. M. Davidson has been throughout

anything but optimistic about the outcome. However, there is no doubt at all that he has secured a few years of benefit.

There is also in our series one case of *Felty's syndrome* (Fig. 8), referred by Dr. G. A. Emmerson, of the Royal West Sussex Hospital, Chichester. This condition is characterized by rheumatoid



A



B

FIG. 8.—Felty's syndrome. A, Enlarged spleen, enlarged liver, and chronic rheumatoid arthritis. The patient also had Sjögren's disease.

arthritis, neutropenia, and a large spleen. After a trial with cortisone, which did not affect the blood picture, though it reduced the pain of the rheumatism, splenectomy was performed. Previous to operation, the W.B.C. were 1,100, the lymphocytes 75%, and the neutrophils 4%. Now, two years later, the W.B.C. are 6,100, and the neutrophils 39%, and the patient says she is better than she has been for years. She is, however, an extremely nice person and very anxious to please.

(4) PANCYTOPENIA

Primary hypersplenism causing pancytopenia, in which all elements are equally affected, and in which the spleen is large, and in which the bone-marrow is hyperplastic, has been described. One patient, a girl of 24 (Dr. R. S. Bruce Pearson's patient), possibly fits into this category. Splenectomy was performed over four years ago now, and she slowly, though steadily, improved in health as a result. To-day she is quite well, with a daughter aged 6 months.

SECONDARY HYPERSPLENISM AND MISCELLANEOUS

There were 21 patients in whom splenectomy was performed, chiefly for secondary hypersplenism, i.e. in patients known or thought to have incurable disorders, but in whom removal of the spleen might be of benefit.

Operation on these conditions must of necessity be somewhat empirical, and in some cases was performed more in the spirit of hope than belief. I would like to comment on three of these conditions.

(i) *Porphyria Congenita*

Since birth, the patient, a boy, had passed orange-coloured urine, and the deciduous teeth were pink. During infancy, dermatitis during the summer months led to scarring of the exposed parts, and slow mass destruction of the tissues. The sight of one eye was lost. The appearance of the face and hands before operation is shown in Fig. 9 (A and B). Splenectomy was performed when the patient was 34 years of age at Professor C. H. Gray's request (a) because there was evidence of latent (or subclinical) haemolysis, and (b) because there was some reason to hope that removal of the spleen might lead to production of Type III porphyrins in normal amounts, and to an end of production of Type I porphyrins which were responsible for the condition of the skin.

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FIG. 9.—A and B, Face and hands of a patient suffering from porphyria congenita. For details see text. By kind permission (1951) *Lancet*, ii, 603, 604.

The experiment failed. Eighteen months after operation the patient died from renal failure due to chronic nephritis.¹

(ii) *Aplastic Anaemia*

The response to splenectomy has on two occasions been phenomenal and quite unexpected. The operation was performed because the patient was going downhill in spite of every care. It was argued that splenectomy would do little harm, and might, in fact, do good. One was the boy, aged 12, previously mentioned, for whom exploration was made because of pain; and another boy of 20, operated upon in 1930 who in 1938 was known to be perfectly well (Dr. A. Gilpin's patients). On the other hand, a child of 3 years, with an unusual and variable bone-marrow finding, once showing hypoplasia of the red cells only, and once, hyperplastic changes, failed to improve at all after removal of an enlarged spleen. One other patient died three days after operation. He was 64. As far as I know, splenectomy can only be recommended when the patient fails to respond to conservative measures. It would appear to be quite impossible to predict the result in any given case.

(iii) *Myelosclerosis (Myelofibrosis)*

In this condition, in which the bone-marrow is slowly obliterated by osteoid or fibrous tissue, the spleen may again take on its prenatal function of haemopoiesis. The liver may also show metaplasia. The spleen becomes enlarged, sometimes *enormously*, and the rate of destruction of red cells is correspondingly increased, so that the patient becomes increasingly anæmic, and blood transfusions have to be more and more frequently administered in ever greater quantities. The question is—should splenectomy be undertaken to stay this excessive haemolysis—or should the spleen be preserved, as it is taking over the haemopoietic function of the bone-marrow? It has been stated authoritatively that on *no account* should the spleen be removed—that to do so would be disastrous. But our experience shows that this opinion is perhaps too emphatically stated. We have transgressed the law on three occasions. Our action seemed well justified in the case of two survivors of the operation. The first case was (Dr. A. Gilpin's patient) in 1942, and the blood condition had greatly improved within six months, but a further follow-up was not possible after that time. In the second (Dr. J. L. Livingstone's case), operation converted a bedridden patient incapacitated by his huge spleen, which weighed 8 lb. 12 oz. after removal, into a man who did a full day's work five days a week (Fig. 10). He came into hospital thereafter every five to six weeks to be given blood, and lived in comparative comfort for two

¹The case has been presented in detail by C. H. Gray and A. Neuberger in the *Lancet* (1952) i, 851.

years and five months, eventually dying in hospital with bronchopneumonia. At post-mortem the liver was found to be enormously enlarged. Active hæmopoiesis of all three elements was taking place within it, and also in the abdominal lymph glands. Also to a lesser extent in the kidneys. Another example of the truth that one cannot subdue the reticulo-endothelial system.



FIG. 10.—Incision. The white line runs parallel to the scar. Nineteen months before this photograph was taken, a spleen weighing 8 lb. 12½ oz. had been removed for myelosclerosis.

THE OPERATION

I remember listening in the thirties to an entrancing address on the spleen by the late Sir David Wilkie, at a meeting of the Medical Society of London. Very shortly afterwards I went to Edinburgh to see Mr. Wilkie, as he then was, do a splenectomy on a young man with acholuric jaundice. There were two steps which he stressed as necessary before attempting to deliver the spleen. They are: (a) To tie or put a temporary clip on the splenic artery after exposing it through the left aspect of the gastrocolic omentum, and then (b) to divide the lieno-renal ligament with a knife or by diathermy under vision. He had had a long Bard Parker handle specially made for this purpose. I am glad to have an opportunity of recalling Wilkie's technique to mind, because two or three years ago, on the very same rostrum from which he had spoken, it was said that he advocated tearing blindly through the lieno-renal ligament with the fingers.

All these 71 splenectomies in this list were performed through the abdomen, although I do not doubt that a thoracic approach might have made the actual operation easier in some instances. Unless one wishes to examine the gall-bladder, one uses a left oblique incision, extending it to cut through the right rectus if the spleen is a very big one (Fig. 10).

The oblique incision gives a much better scar than does the vertical. This was brought to my notice some years ago when I was examining young patients after splenectomy—some of whom were related. The "straight" cases were a little disgruntled because the "oblique" ones had nicer looking stomachs!